Palladium-Catalyzed Alkene Difunctionalization Reactions: Synthesis of Functionalized Carbocycles and Mechanistic Investigation

by

Evan Clay Bornowski

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Doctoral Committee:

Professor John P. Wolfe, Chair
Professor Adam Matzger
Associate Professor Pavel Nagorny
Assistant Professor Alison R. H. Narayan

Evan C. Bornowski

bornowec@umich.edu

ORCID iD: 0000-0002-6119-5521

Dedication

For it is by grace you have been saved, through faith – and this is not from yourselves, it is the gift of God – not by works, so that no one can boast.

Ephesians 2:8-9

Acknowledgements

"'Vanity of vanities,' says the preacher. 'All is vanity.'"

The Lord. Long after no one remembers these words, Your words will remain. So, thank you. Thank you for saving me and being the only thing in the world that is not vanity. I am proud of this accomplishment, but I consider it meaningless in comparison to grace. Thank you.

Professor John P. Wolfe. You are, simply put, the best. I could not have asked for a better advisor and mentor. That steel trap you call a memory is truly inspirational. Thank you for providing an environment for me to learn and grow. Thank you for always being available to talk about chemistry or just life in general. Graduate school can be a grind, but, more often than not, the culture you cultivated in your lab made the experience enjoyable. Thank you for not kicking me out of the lab when I gave terrible presentations or when the Packers beat the Lions. I will miss the trips to the bar before poster sessions and hearing stories about all the famous chemists you have met. Thank you for driving to the middle-of-nowhere Wisconsin to celebrate my wedding. I owe a lot to you and my time in the Wolfe Pack. "Thank you" seems too little, but nevertheless, thank you.

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in your lab. I learned more in a four-month rotation in your lab than all four years in undergrad. I will always be grateful to you for the opportunity you gave me. Thank you all for the knowledge, skills, and support you have invested in me. Thank you.

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My parents. I remember the Easter morning service when I told you I knew Michigan was the right place for me. Thank you for being more excited for me than I am back then and now. Thank you for being there since, quite literally, the very beginning. You are awesome scientist parents and growing up it was an absolute joy to learn from you both at Preble. Dad, since I have a PhD now, can I finally shop showing my work on unit transfer and mole problems? Thank you for reminding me to work hard, relax a little when able, and to trust and love Jesus. Wonderful parents are not guaranteed, and I am so thankful you love and support me through everything, even through the infamous pink puff paint mechanism presentation. Thank you for the thousands of hours of talks in the lab. Thank you for taking me fishing. I love you both very much. Thank you.

My grandparents. Thank you for being my biggest fans. Grandma, I am sorry you cannot see me graduate. I miss you every day. Grandpa, thank you for sharing your wisdom with me. Especially the stories about walking to and from school uphill both ways in 15 feet of snow. Memories make us rich, and I am the richest person in the world because of you two. Thank you.

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Elsa. Thank you for showing me the ropes in the lab. I learned a ton from your mentorship. I always loved our conversations about Disney, life, and lab. Thank you for your patience and support. Thank you.

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Wolfe Pack. Thank you all for accepting me into the lab. Thank you, Derick White, for all the professional advice and excellent chemistry to build from. Thank you to Jordan Boothe and Zach Garlets for being examples of excellent chemists. Thank you to all the undergraduate and graduate students I mentored for all their hard work: Taylor Morgan,

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Camp family and D&D adventurers. Trevor Schmitz, Alex Eggen, Lukas Powers, Nathan Eggen, and Taylor Gillespie, your friendship is the world to me. Thank you for all the crazy late nights and epic adventures. I do not have a lot of friends, but the ones I do have are of the highest quality. I love you all and thank you.

Nolan Bornowski and Logan Bornowski. Thank you for being two loveable goofballs and supporting me the past five years. Thank you for being excellent players in our campaign so I can lose myself in a fantasy game. Thank you for standing with me on my wedding day and thank you for standing with me now. I love you both very much and am forever grateful for all the strange ways you both show me you love me. Thank you.

ULC family. Thank you for sharing Jesus with me every week. Thank you to Pastor Gabe Kasper and Pastor Marcus Lane for helping my spiritual growth and always keeping the focus on Jesus. Thank you to my community group, Heather and Mark Symons, Garret and Corrine Lenz, and Zach and Dakota Hiller for welcoming Jessica and me to Ann Arbor and into your lives. We love you all very much. Thank you.

There is, undoubtedly, at least a legion more to thank (see reference: a cliché about children and villages). I could not have completed this work without significant buy-in and investment from everyone surrounding me these past 27 years. I am a product of

countless interactions, big and small, and I want to say a general thank you to everyone who shares in my life. I would not be here without all of you. Thank you.

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List of Abbreviations

α ..... alpha

acac ..... acetylacetone

acac [$Pd(acac)_2$] ..... acetylacetonate

Ag ..... silver

Ar ..... aryl (when bound to another atom)

Au ..... gold

β ..... beta

Boc ..... *tert*-butyloxycarbonyl

Bn ..... benzyl

Br ..... bromide

Bz ..... benzoyl

calcd ..... calculated

C ..... carbon

Cl/Cl^- ..... chloride

CN ..... cyano

Co ..... cobalt

Cp ..... cyclopentadienyl

Cs ..... cesium

Cu ..... copper

$CuCl_2$ ..... copper(II) chloride

Cy ..... cyclohexyl

°C ..... degrees Celsius

d ..... doublet

D ..... deuterium

dba ..... dibenzylideneacetone

DCE 1,2-dichloroethane

DCM ..... dichloromethane/methylene chloride

dd ..... doublet of doublets

ddd ..... doublet of doublet of doublets

ddt ..... doublet of doublet of triplets

dt ..... doublet of triplets

dq ..... doublet of quartets

DMF ..... dimethylformamide

dppe ..... 1,2-bis(diphenylphosphino)ethane

dppf ..... 1,1'-bis(diphenylphosphino)ferrocene

dppBz ..... 1,2-bis(diphenylphosphino)benzene

dr ..... diastereomeric ratio

η ..... eta

equiv ..... equivalents

eq ..... equation

er ..... enantiomeric ratio

ESI ..... electrospray ionization

Et ..... ethyl

Eu ..... europium

F ..... fluoride

Fe ..... iron

g ..... gram(s)

h ..... hour(s)

H^+ ..... proton

H_2O ..... water

HRMS ..... high resolution mass spectrometry

Hz ..... hertz

I ..... iodide

^{i}Pr ..... isopropyl

IR ..... infrared spectroscopy

LiHMDS/KHMDS ..... lithium/potassium hexamethyldisilazide

J ..... coupling constant

L ..... liter(s)

Li ..... lithium

LDA ..... lithium diisopropylamide

L_n/L ..... general ligand

LG ..... leaving group

M ..... molar (mol/L)

m ..... multiplet

Me ..... methyl

$MgSO_4$/$NaSO_4$ ..... magnesium sulfate/sodium sulfate

mol ..... mole

MOM ..... methoxymethyl

mp ..... melting point

MS ..... molecule sieve

N/N_2 ..... nitrogen

Na ..... sodium

n-BuLi ..... butyllithium

NMR ..... nuclear magnetic resonance

NO_2 ..... nitro/nitrite

Nuc/Nuc-H ..... nucleophile

O/O_2 ..... oxygen

OAc ..... acetate

OH ..... hydroxide

OMe ..... methoxy

O^tBu ..... *tert*-butoxide

O^iPr ..... *iso*-propoxide

OTf ..... triflate

p ..... para

Pd ..... palladium

P ..... phosphorus

p ..... pentet

π ..... pi

Ph ..... phenyl

$PhCF_3$ ..... trifluorotoluene

$PhCH_3$ ..... toluene

PMP ..... para-methoxyphenyl

q ..... quartet

R ..... general functional group

rt ..... room temperature

Ru ..... ruthenium

s ..... singlet

Sn ..... tin

t ..... triplet

t ..... tert

^{t}butyl/^{t}Bu ..... *tert*-butyl

TBS ..... *tert*-butyldimethylsilyl

Temp ..... Temperature

TES ..... triethylsilyl

Tf ..... triflyl

TFA [$Pd(TFA)_2$] ..... trifluoroacetate

TFA ..... trifluoroacetic acid

Tf_2O ..... triflic anhydride

THF ..... tetrahydrofuran

T. S..... transition state

R..... general functional group

X..... general halide, counterion, or atom

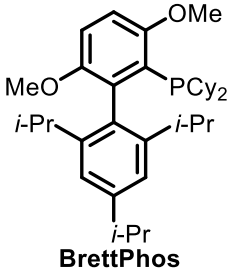
Y..... general heteroatom

Z..... general atom or substitution

List of Ligands

The ligands drawn in this section are referenced by name throughout this dissertation. They are illustrated here for the reader's convenience.

Buchwald Ligands



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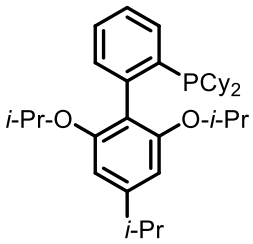

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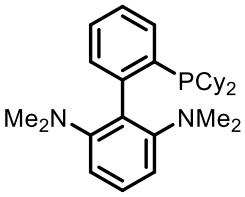

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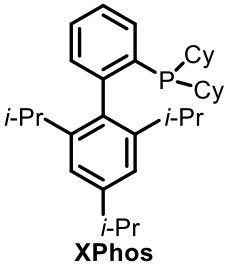

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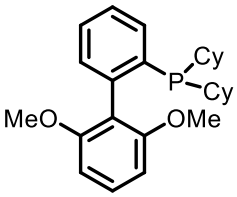
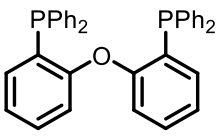


SPhos

Bidentate Ligands



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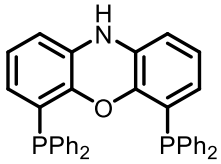
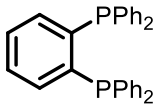


***N*-Xantphos**



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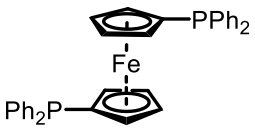

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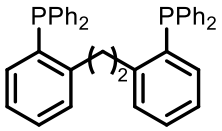

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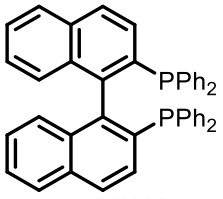
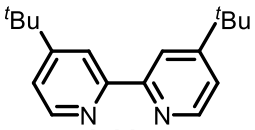


rac-BINAP



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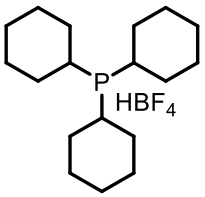
Monodentate Ligands



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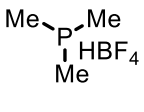

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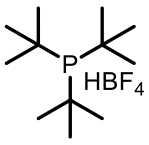

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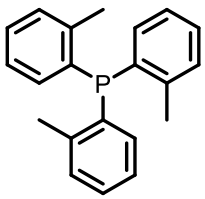

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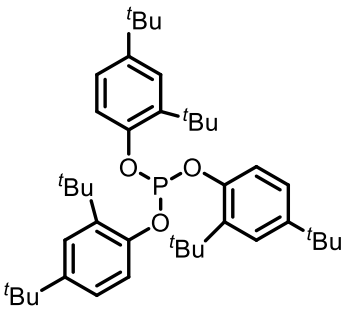


P(-2,4-*t*Bu-OC$_6$H$_3$)$_3$

Abstract

Metal-catalyzed alkene difunctionalization reactions have given chemists powerful tools to quickly increase the chemical complexity of molecules in a single step. This dissertation focuses on the development of new Pd-catalyzed alkene difunctionalization reactions for the construction of functionalized carbocycles. Specifically, treatment of 2-allylphenyl triflate, or related acyclic 1,5-dienyl triflates, with enolate nucleophiles in the presence of a palladium catalyst and a base generates either four- or five-membered carbocyclic products. These reactions form two new bonds and a ring in a single transformation, with generally high levels of diastereoselectivity. The reactions described in this dissertation provide new and important methodology for the synthesis of functionalized carbocycles.

Previous work in the Wolfe lab, as described in Chapter 1, laid the foundation for coupling reactions between exogenous nucleophiles and aryl or alkenyl bearing tethered alkenes. These studies focused on the use of nitrogen, oxygen, and indole nucleophiles, which were incorporated into the carbocyclic products. In Chapter 2, my work details a significant expansion of nucleophile scope by incorporating stabilized carbanions, including malonates, esters, and ketone enolates, as exogenous nucleophiles in our Pd-catalyzed alkene difunctionalization reactions. The products of these reactions are formed in good yields and good diastereoselectivity, >20:1 relative to the bridging carbon when utilizing alkenyl triflates as the coupling partner. The mechanism of reaction is proposed

to go through a Pd(0)/Pd(II) cycle that involves oxidative addition of the aryl/alkenyl triflate to Pd(0), followed by *anti*-carbopalladation and subsequent reductive elimination.

My work has also included development of a regiodivergent variant of our Pd-catalyzed alkene difunctionalization reactions, as described in Chapter 3. Alkenyl triflates, with geminal "R" groups relative to the vinyl triflate, bearing tethered alkenes were coupled with malonate nucleophiles for the formation of either methylene cyclobutanes or methylene cyclopentanes. Two unique catalyst systems were employed to select for the desired regioselectivity. The mechanism governing the formation of the cyclopentane product appears to be analogous to our previous reported Pd(0)/Pd(II) cycle and described above. Preliminary mechanistic studies involving the synthesis of a deuterated alkene starting material and its stereoselective reaction with diethyl malonate suggest the four-membered ring products are formed by oxidative addition followed by a *syn*-migratory insertion and subsequent stereo-retaining, reductive elimination from the metal center. To the best of our knowledge, this is the first example of an sp^3-sp^3 C-C bond forming reductive elimination from Pd(II) with a malonate nucleophile.

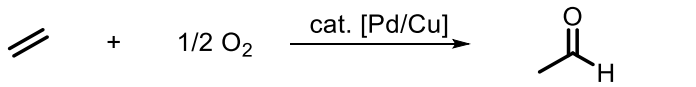
Additional scope and studies of Pd-catalyzed alkene difunctionalizations are described in Chapter 4. Preliminary results incorporating exogenous nitrile nucleophiles as coupling partners are described. Preliminary results utilizing nitrogen nucleophiles in the regiodivergent Pd-catalyzed cyclization are described. Lastly, preliminary efforts to construct heterocycles with exogenous nucleophiles as coupling partners are described.

Chapter 1

Introduction to Palladium-Catalyzed Alkene Difunctionalization Reactions

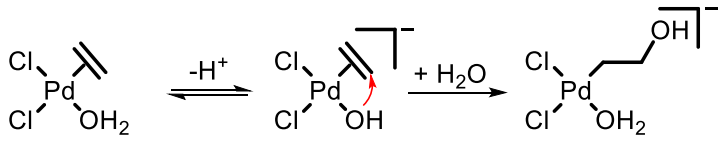
1.1 The Wacker Reaction

Starting in the mid-20th century, the discovery and development of catalytic reactions of alkenes transformed the landscape of organic chemistry. Specifically, in 1959 the Wacker process (or Wacker reaction) made significant improvements upon the already established stoichiometric oxidation[1] of ethylene to acetaldehyde by developing a catalytic variant (eq 1-1).[2,3,4] The innovative difference between stoichiometric and catalytic being the incorporation of cocatalytic $CuCl_2$ salts along with molecular oxygen to

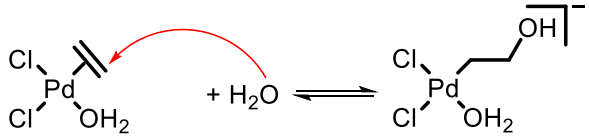


(eq 1-1)

oxidize the palladium catalyst and thus turnover the catalytic cycle (**Scheme 1-1**). The crucial hydroxypalladation step of the Wacker reaction has been the center of controversy for the past six decades. The major focus of the debate is centered upon the modality of nucleophilic addition step; whether the reaction proceeds through a *syn*-addition hydroxypalladation (eq 1-2) or an *anti*-addition hydroxypalladation (eq 1-3) step. The following investigations into the mechanism of the Wacker reaction have proven

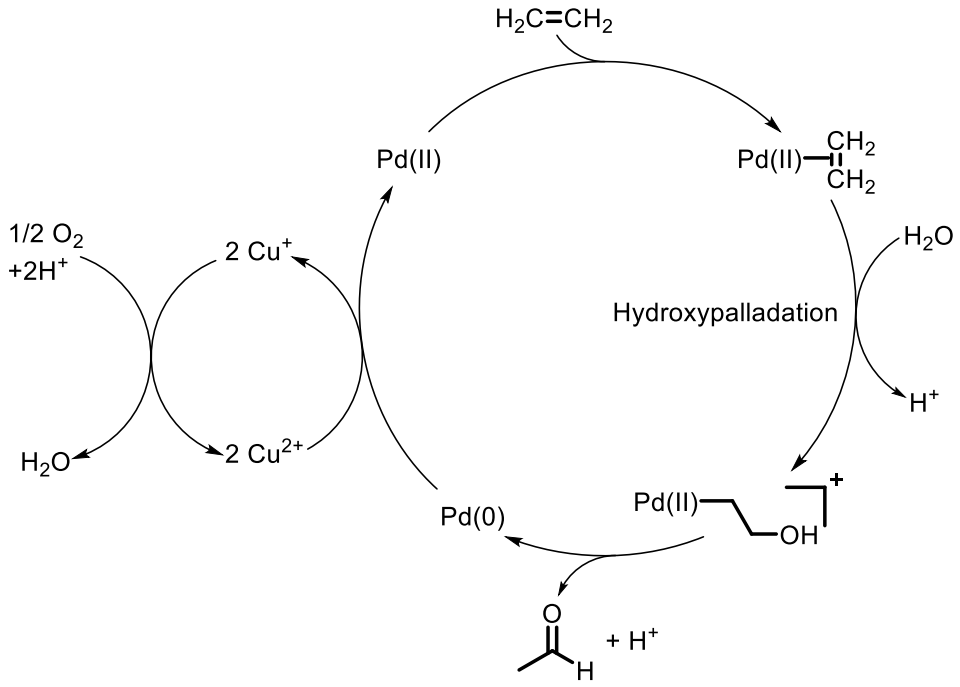


(eq 1-2)



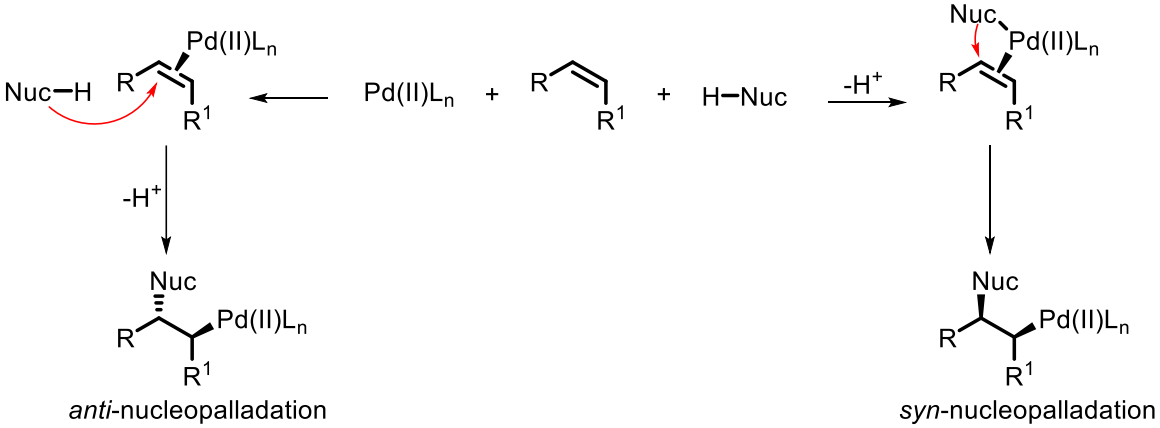
(eq 1-3)

Scheme 1-1: The Wacker reaction



fundamental to determining which influences impact nucleopalladation and how those factors determine the overall course of the reaction.[4] Additionally, understanding the Wacker reaction is an important step to understanding and manipulating similar reaction mechanisms and other processes sensitive to diverse reaction conditions. Understanding the process and factors contributing to the hydroxypalladation step in the Wacker reaction was, and is, one of the first steps in understanding nucleopalladation step of palladium-catalyzed alkene difunctionalization reactions as shown in **Scheme 1-2**.[5]

Scheme 1-2: Stereochemical pathways of nucleopalladation



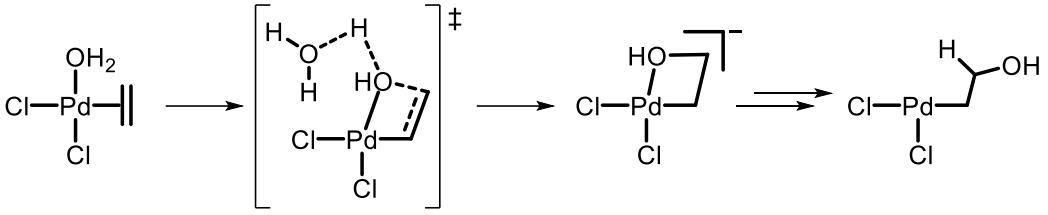
1.2 *Syn*- vs *Anti*-Oxypalladation Pathways of the Wacker Reaction

There has been extensive study done upon the Wacker reaction. Although improved, there yet remains an imperfect view of the mechanism governing the hydroxypalladation.[4] Foundational work by Henry provided strong kinetic support for a *syn*-addition pathway.[6] These kinetic studies found that nucleophilic attack of external hydroxide on the η^2 alkene Pd(II) complex would require a biomolecular reaction to proceed faster than diffusion, ruling out such an attack. Following those studies, several groups including Stille,[7] Bäckvall and Åkermark,[8] and others[9] developed experiments to probe the stereochemistry of the oxypalladation of alkenes. These studies provided evidence for the *anti*-addition pathway; however, due to acetaldehyde being achiral, the experiments necessitated a fundamental change in substrate by utilizing allyl alcohols to instill chirality. Additionally, the authors significantly altered the overall reactions conditions from the original Wacker reaction by including a carbon monoxide atmosphere and high chloride ion concentrations. Therefore, while providing strong evidence for an *anti*-addition mechanism in their new oxypalladations, their evidence was of limited use in conclusively labeling the hydroxypalladation step of the original Wacker reaction as an *anti*-addition. Henry and co-workers later provided substantial evidence that showed varying reaction conditions from the industrial Wacker conditions (including carbon monoxide and increasing [Cl^-]) resulted in a switch in mechanism in the hydroxypalladation.[10] Henry and co-workers showed oxypalladation to proceed through a *syn*-addition pathway at low [Cl^-] and through an *anti*-addition pathway at high [Cl^-].

Computational studies by Goddard, Oxgaard, and co-workers have added support to this finding. Goddard and co-workers also proposed the energy barrier for *syn*-

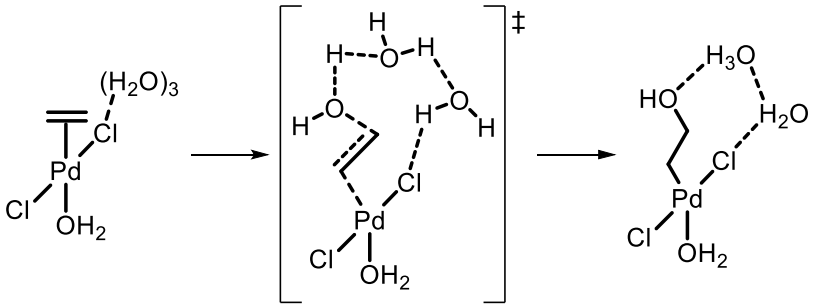
hydroxypalladation to be far too high to be feasible. However, as shown in **Scheme 1-3**,

Scheme 1-3: *Syn*-hydroxypalladation assisted by hydrogen bonding



Goddard and co-workers presented an energetically acceptable alternative pathway to equilibrium deprotonation where the η^2 metal complex may undergo an inner-sphere transfer of a water molecule while simultaneously ejecting a proton into the solvent.[11] Other experimental studies[12] and computational studies[13] have provided additional support for an *anti*-addition hydroxypalladation mechanism, albeit in a modified mechanism involving a three-water hydrogen-bond bridged chain (**Scheme 1-4**).[12] Taken

Scheme 1-4: *Anti*-hydroxypalladation assisted by hydrogen bonding



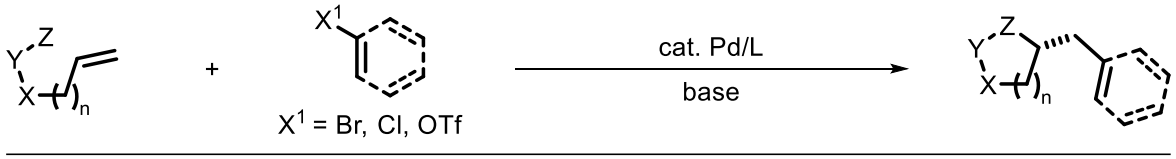
as a whole, the thorough investigations into oxypalladation highlight the extreme sensitivity of the mechanism of reaction to the employed catalyst, substrate, and overall reaction conditions.

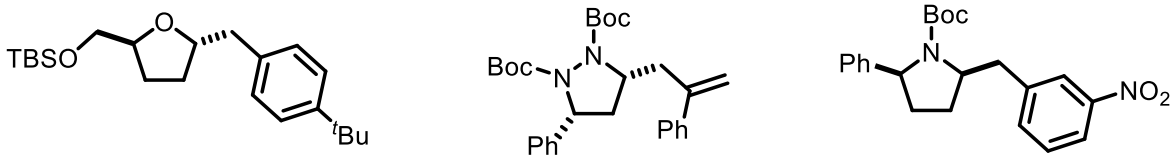
1.3 Development of Palladium-Catalyzed Alkene Difunctionalization Reactions for the Construction of Functionalized Carbocycles

Since 2004 our group has developed and investigated a series of alkene difunctionalization reactions between aryl or alkenyl halides or triflates, and alkenes bearing tethered nucleophiles.[14,15] As shown below (**Scheme 1-5a**), these transformations affect the formation of one carbon-heteroatom bond, one carbon-carbon

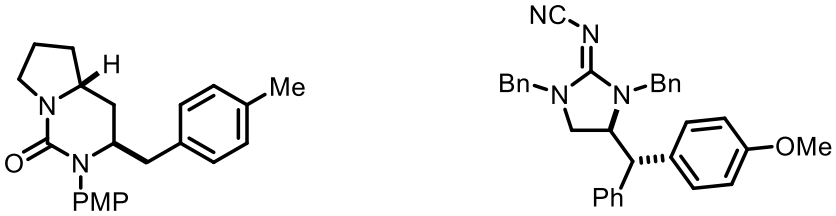
Scheme 1-5: Synthesis of heterocycles

a) Coupling of unsaturated nucleophiles and aryl/alkenyl electrophiles



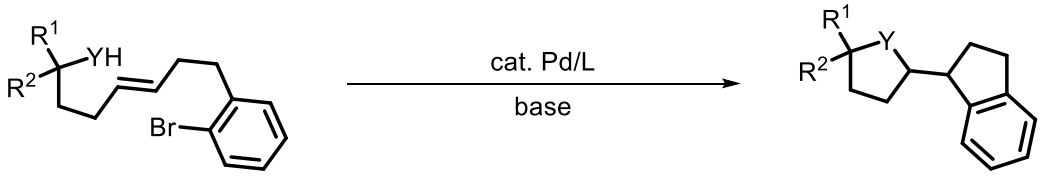


68% (>20:1 dr) 63% (11:1 dr) 75% (>20:1 dr)



70% (>20:1 dr) 75% (>20:1 dr)

b) Fully intramolecular reactions



R^1, R^2 = Me, Y = O: 50%, >20:1 dr

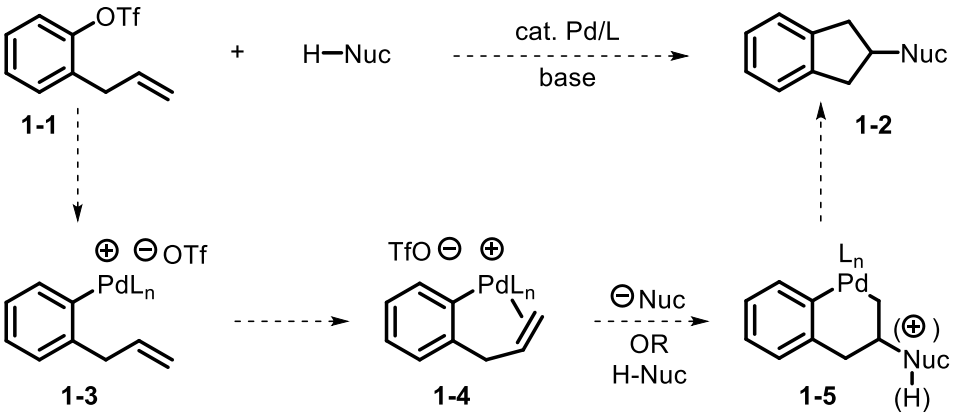
R^1, R^2 = H, Y = NPh: 71%, >20:1 dr

bond, and up to two stereocenters. The transformations afford an array of heterocyclic products, including tetrahydrofurans,[16] pyrazolidines,[17] pyrrolidines,[18] cyclic ureas[19] and cyclic guanidines,[20] in good yield and high diastereoselectivity.

We have also examined fully intramolecular variants of these transformations (**Scheme 1-5b**),[21] and have demonstrated that products resulting from either *syn*- or *anti*-addition to the alkene can be selectively obtained with suitable substrates and conditions.[19e,21,22] These reactions proceed via a mechanism involving oxidative addition of the electrophile to Pd(0), followed by either *syn*- or *anti*-nucleopalladation[5,23] of the

alkene (depending on substrate and conditions), and then C–C bond-forming reductive elimination.[14,24]

Scheme 1-6: Planned synthesis of carbocycles



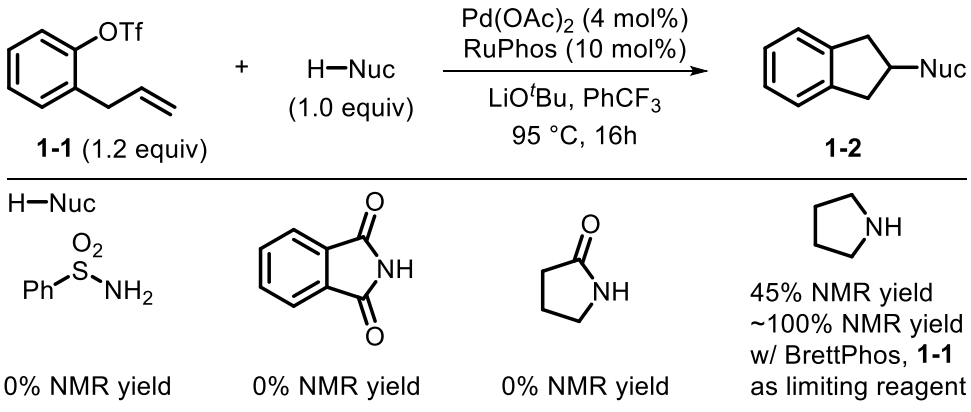
Although the transformations described above provide a straightforward means of accessing several different heterocyclic ring systems, in all cases the alkene was tethered to the nucleophilic component of the coupling reaction. Several years ago, Dr. Derick White, a former Wolfe group co-worker, reasoned that by changing the arrangement of the pieces (alkene, nucleophile, and electrophile) such that the alkene was tethered to the electrophile, we could develop a new method for the synthesis of functionalized carbocycles. As shown in **Scheme 1-6**, the coupling of 2-allylphenyltriflate **1-1** (or related congeners) as the electrophile, combined with an external nucleophile (either anionic or neutral, depending on pK_a considerations; nucleophiles such as amines are likely deprotonated after the nucleopalladation step), should provide carbocyclic products **1-2**. Oxidative addition of the electrophile to Pd(0) would provide complex **1-3**, which can undergo coordination of the alkene to Pd, followed by attack of **1-4** by the external nucleophile to afford **1-5** (which may be protonated/ charged, or neutral, depending on the nucleophile). Reductive elimination from **1-5** would then give **1-2**. **Sections 1.4-1.9**

summarizes our progress thus far (2015-present) on the development of this new class of alkene difunctionalization reactions.

1.4 Optimization of Exogenous Nitrogen Nucleophiles

In preliminary studies, Dr. White and Dr. Hutt sought to establish proof-of-concept results for the general transformation outlined above. As such, they elected to examine the Pd-catalyzed coupling of 2-allylphenyl triflate (**1-1**, prepared in one step from commercially available 2-allylphenol) with nitrogen nucleophiles (**Scheme 1-7**). Initial attempts to couple 1.0 equiv. of benzenesulfonamide, phthalimide, or pyrrolidine-2-one with 1.2 equiv. of **1-1** in the presence of a $Pd(OAc)_2$/RuPhos[25] catalyst system were unsuccessful. However, use of pyrrolidine as the nucleophile afforded product **1-2** in 45% yield. After further optimization we found that the desired product **1-2** was obtained in essentially quantitative yield (NMR) when BrettPhos was employed as ligand with 2-allylphenyl triflate as the limiting reagent instead of the amine nucleophile (1.0 equiv. **1-1**, 1.2 equiv. amine).[26]

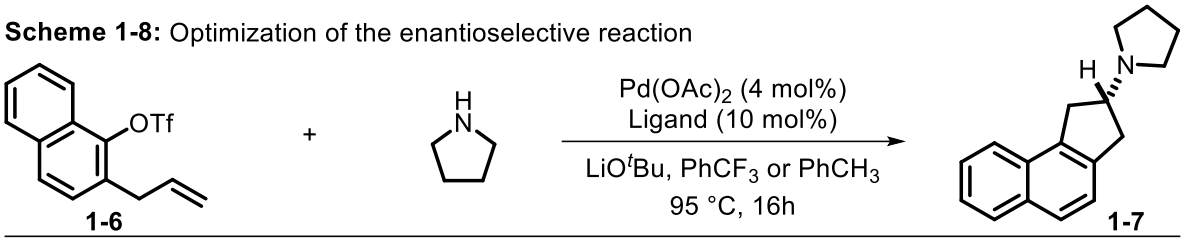
Scheme 1-7: Preliminary experiments and proof-of-concept

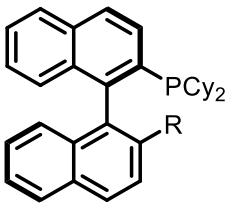


1.5 Enantioselective Reactions of Aryl and Alkenyl Triflates with Nitrogen Nucleophiles

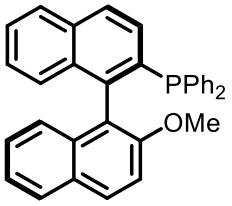
Once Dr. White and Dr. Hutt had successfully demonstrated the desired reactivity, they elected to explore enantioselective variants of this reaction, rather than simply elucidate

Scheme 1-8: Optimization of the enantioselective reaction

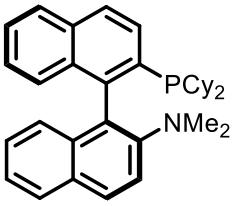




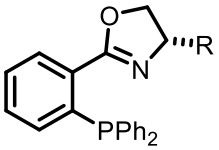
1-L1: R = OMe; 82:18 er
1-L2: R = O*i*Pr; 69:31 er



1-L3: 52:48 er



1-L4: 13:87 er

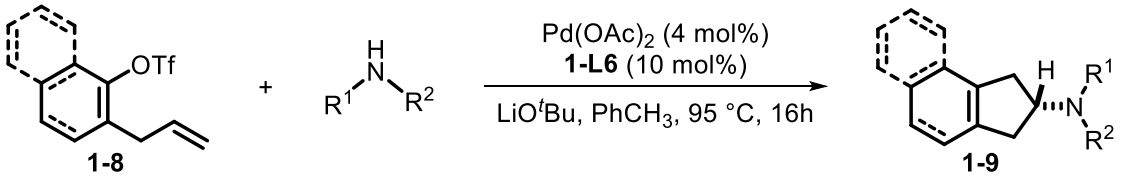


1-L5: R = *i*Pr; 88:12 er
1-L6: R = *t*Bu; >99:1 er
98% yield

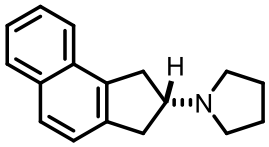
the scope of the racemic transformation. As such, they examined the coupling of naphthyl triflate **1-6** with pyrrolidine using a chiral palladium catalyst system (**Scheme 1-8**).[26] They initially examined binaphthyl derived monodentate phosphines and obtained promising results of up to 87:13 er for product **1-7** but could not optimize beyond that point. After exploration of a few alternative ligand scaffolds, they discovered that phosphinooxazolines (PHOXtype ligands)[27] also provided interesting levels of asymmetric induction, and eventually found that *tert*-butyl phosphinooxazoline ligand **1-L6** provided the desired product **1-7** in 98% yield and >99: 1 er.[28]

With satisfactory conditions in hand, they proceeded to explore the scope of the asymmetric alkene carboamination reactions. As shown in **Scheme 1-9**, the transformations were effective with both cyclic and acyclic secondary amines, providing good to excellent enantioselectivity. Modest yields and lower levels of asymmetric induction were obtained in the reactions of acyclic secondary amine nucleophiles (diethylamine and *N*-methylbenzylamine). Primary amine nucleophiles were also coupled in moderate to good yield and high enantioselectivity. Simple 4-substituted 2-allylphenyl triflates, along with alkenyl triflates derived from α-tetralone, proved to be suitable

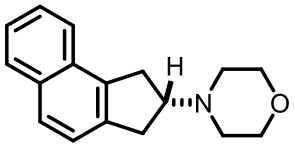
Scheme 1-9: Enantioselective alkene carboamination reactions



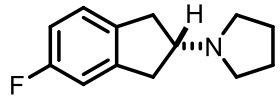
Representative Examples



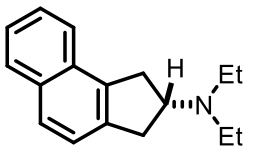
1-9a: 98%, >99:1 er



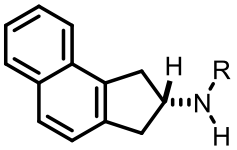
1-9b: 88%, 95:5 er



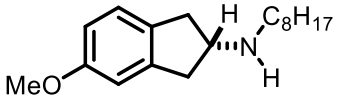
1-9c: 77%, 98:2 er



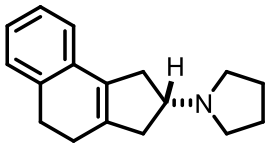
1-9d: 47%, 89:11 er



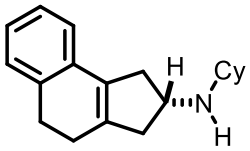
1-9e: R = Cy: 63%, >99:1 er
1-9f: R = *n*-octyl: 82%, 97:3 er



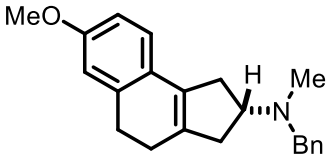
1-9g: 59%, >99:1 er



1-9h: 69%, 98:2 er



1-9i: 41%, 98.5:1.5 er



1-9j: 50%, 85:15 er

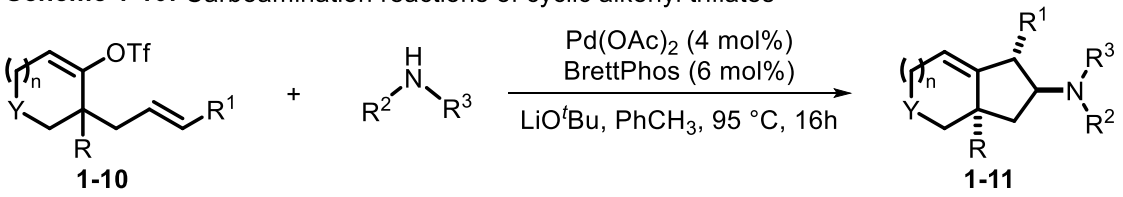
substrates in addition to the naphthyl triflate. Although enantioselectivities were comparable for both aryl and alkenyl triflates, the chemical yields obtained in reactions of alkenyl triflates were generally lower than those for couplings involving aryl triflates.[29] Their current experimental evidence supports for their initial mechanistic hypothesis described above in **Section 1.3**, **Scheme 1-6**. In the case of amine nucleophiles, deprotonation likely occurs after, rather than before, the aminopalladation step in the catalytic cycle. Additional discussion of the mechanism and stereochemical outcomes of these general classes of reactions is provided below in **Section 1.9**.

1.6 Diastereoselective Reactions of Alkenyl Triflates with Nitrogen Nucleophiles

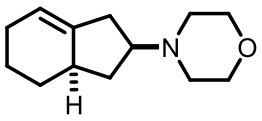
Given the successful enantioselective reactions of alkenyl triflates described above, it seemed likely that several other alkenyl triflates may prove suitable substrates for these reactions. In addition, these reactions could potentially provide access to synthetically useful partially saturated carbocyclic structures. As such, Dr. White began to explore diastereoselective reactions of simple alkenyl triflates **1-10** generated from 2-allylcycloalkanones, which could be prepared in two steps from commercially available materials using straightforward chemistry.[29]

Fortunately, very little optimization was required. The conditions employed for the asymmetric reactions, except using BrettPhos as ligand, provided satisfactory results in these transformations (**Scheme 1-10**). The reactions were effective with a range of

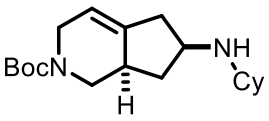
Scheme 1-10: Carboamination reactions of cyclic alkenyl triflates



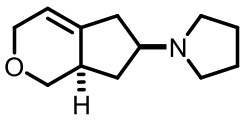
Representative Examples



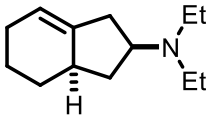
1-11a: 72%, >20:1 dr



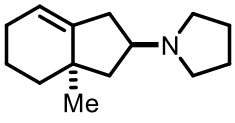
1-11b: 66%, >20:1 dr



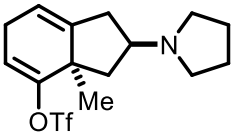
1-11c: 58%, >20:1 dr



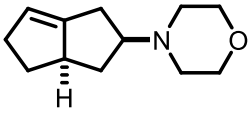
1-11d: 49%, 2.5:1 dr



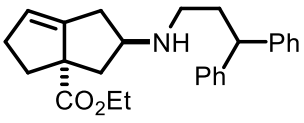
1-11e: 87%, >20:1 dr



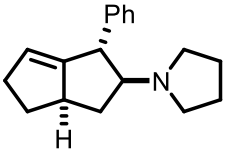
1-11f: 67%, >20:1 dr



1-11g: 71%, >20:1 dr



1-11h: 52%, >20:1 dr



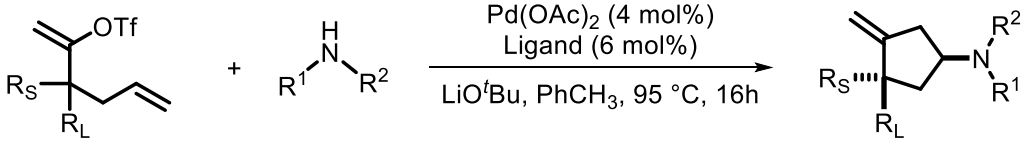
1-11i: 36%, 5:1 dr

primary and secondary amine nucleophiles, and products **1-11** were generated with good to excellent levels of diastereoselectivity. The formation of both 5,5- and 6,5- fused ring systems was feasible, and the presence of an alkyl or ester substituent adjacent to the reactive allyl group was tolerated. In addition, a bis-alkenyl triflate derived from 1,3-cyclohexanedione was converted to aminated bicyclic alkenyl triflate product **1-11f** in 67% yield and >20:1 dr.

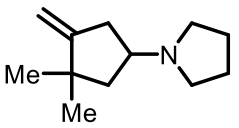
Despite having a reasonably broad scope, the reaction was sensitive to steric effects, as the coupling of the acyclic secondary amine diethylamine proceeded in modest yield (**1-11d**, 49%) and 2.5:1 dr. In addition, when a substrate bearing a 1,2-disubstituted alkene was treated with pyrrolidine, the desired product **1-11i** was formed in only 36% yield and 5:1 dr.

Acyclic 1,5-dienyl triflate substrates **1-12** were successfully converted to exo-methylene cyclopentane derivatives **1-13** in moderate to good yield under the standard reaction conditions (**Scheme 1-11**).[29] However, in contrast to reactions of cyclic alkenyl

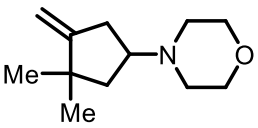
Scheme 1-11: Carboamination reactions of acyclic alkenyl triflates



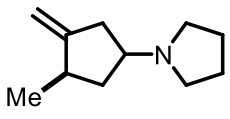
Representative Examples



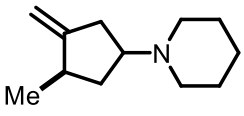
1-13a: 79%
(BrettPhos)



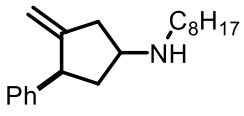
1-13b: 56%
(BrettPhos)



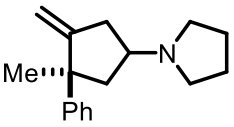
1-13c: 87%, 12:1 dr
(CPhos)



1-13d: 91%, 6:1 dr
(CPhos)



1-13e: 70%, 4:1 dr
(RuPhos)



1-13f: 78%, >20:1 dr
(RuPhos)

triflates **1-10**, the stereocontrol in reactions of the acyclic substrates **1-12** was sensitive to ligand structure. BrettPhos provided only modest diastereoselectivity, but improved results were obtained with the more electron-rich and less sterically bulky biaryl phosphine ligands CPhos or RuPhos. With these ligands the desired products were generated in moderate to excellent diastereoselectivity (4:1 to >20: 1). Discussion of the stereochemical outcome of reactions between alkenyl triflate substrates and various nucleophiles is provided below in **Section 1.9**.

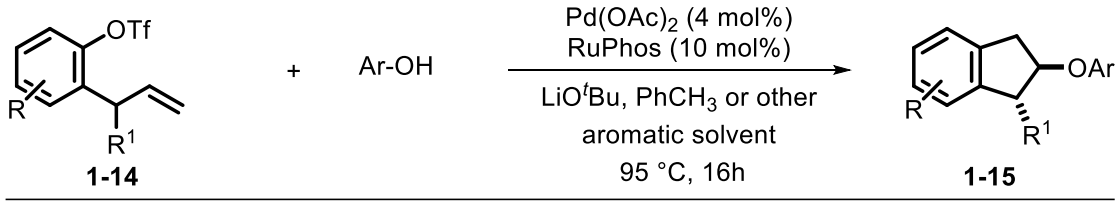
1.7 Diastereoselective Reactions of Aryl and Alkenyl Triflates with Oxygen Nucleophiles

Due to the significance and synthetic utility of O-substituted indane derivatives,[30] Dr. White and co-workers elected to explore alkene difunctionalization reactions involving oxygen nucleophiles, such as phenols or aliphatic alcohols.[31] They initially examined 2-allylphenyltriflate-derived substrates and investigated a broader set of aryl electrophiles than in our earlier studies with amine nucleophiles. Synthesis of substrates **1-14** from the corresponding phenols was straightforward (three steps), and only a slight change to the previously optimized conditions was needed. With RuPhos as the ligand for palladium (in place of BrettPhos), they obtained good yields of products **1-15** for most substrate combinations that were examined (**Scheme 1-12**).

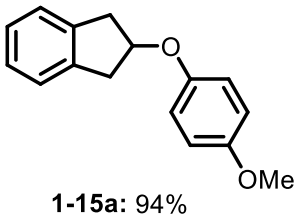
The reactions were effective with a range of phenol nucleophiles, although higher reaction temperatures of 130°C or 160°C were needed with electron-deficient phenols. The presence of an *ortho*-methyl group on both the aryl triflate and the phenol was tolerated (**1-15c**). In addition, a substrate bearing an allylic methyl group was coupled with *p*-methoxyphenol to afford **1-15f** in 98% yield and >20 :1 dr. Interestingly, attempts to affect an enantioselective version of these reactions have thus far been unsuccessful.

The chiral ligand **1-L6**, that provided excellent results with amine nucleophiles (**Scheme 1-9**), failed to promote the coupling of 2-allyl-1-naphthyltriflate with p-methoxyphenol. Only a trace amount of product was formed, and the reasons that **1-L6** does not perform well in this case remain unclear. We have yet to identify a chiral catalyst system that provides both high yield and high enantioselectivity in reactions of oxygen nucleophiles.

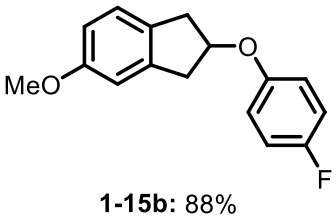
Scheme 1-12: Carboalkoxylation reactions of aryl triflates



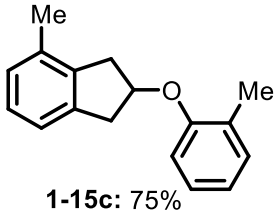
Representative Examples



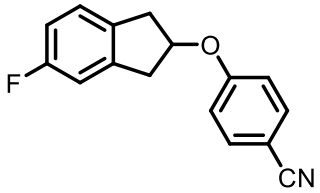
1-15a: 94%



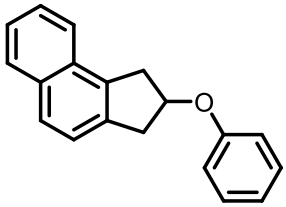
1-15b: 88%



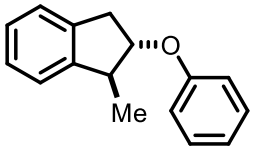
1-15c: 75%



1-15d: 80%



1-15e: 88%

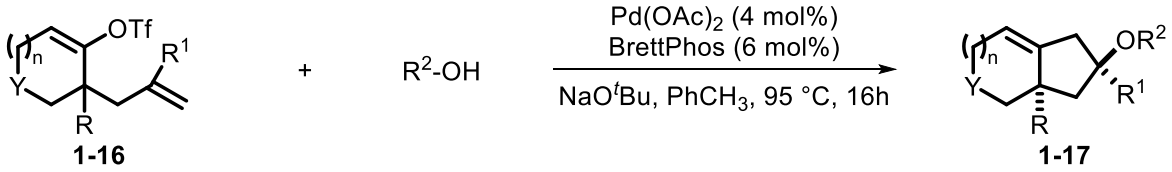


1-15f: 98%, >20:1 dr

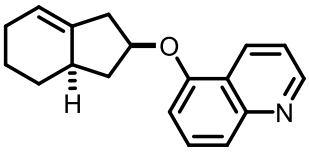
In addition to the aryl triflates described above, a broad series of alkenyl triflate substrates **1-16** proved to be suitable coupling partners with oxygen nucleophiles (**Scheme 1-13**). Both BrettPhos and RuPhos provided good results as ligands for these reactions. In some cases, one of the two was slightly superior to the other, and sometimes NaO^{t}Bu was slightly superior to LiO^{t}Bu. But in many instances, either of the two ligands and bases gave comparable yields of products **1-17**.

The transformations were capable of generating 6,5-fused, 5,5-fused, and 5,5-spiro ring systems in moderate to excellent yields. Diastereoselectivities were very high (>20:1)

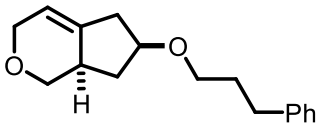
Scheme 1-13: Carboalkoxylation reactions of alkenyl triflates



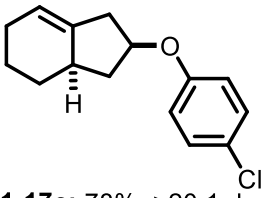
Representative Examples



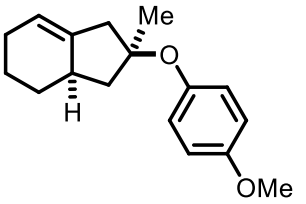
1-17a: 77%, >20:1 dr



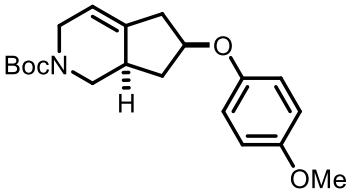
1-17b: 77%, >20:1 dr



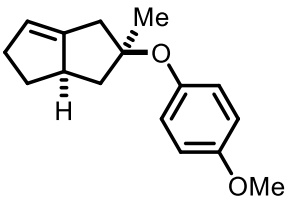
1-17c: 78%, >20:1 dr



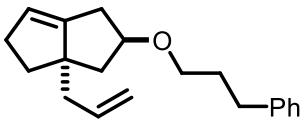
1-17d: 50%, >20:1 dr



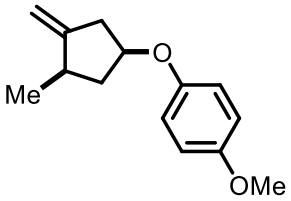
1-17e: 82%, >20:1 dr



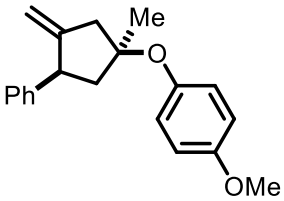
1-17f: 70%, >20:1 dr



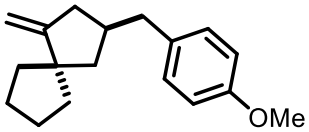
1-17g: 94%, >20:1 dr



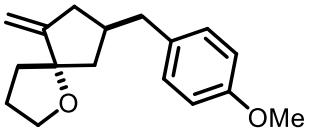
1-17h: 88%, >20:1 dr



1-17i: 56%, >20:1 dr



1-17j: 71%



1-17k: 83%, 5:1 dr

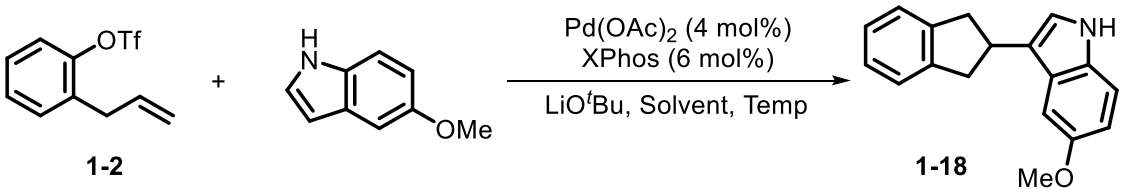
in most cases, and a number of different phenols and aliphatic alcohols could be employed as nucleophiles. Importantly, substitution at the internal alkene carbon of the cyclizing alkene was tolerated. Therefore, the reactions can produce tertiary alkyl-aryl ethers that would be difficult to obtain with other methods.

1.8 Diastereoselective Reactions of Aryl and Alkenyl Triflates with Indole Nucleophiles

In order to further explore the scope and limitations of this class of alkene difunctionalization reactions, Dr. Kirsch and co-workers elected to study reactions of heteroaromatic compounds.[32] They were curious as to whether weak carbon nucleophiles, such as indoles, would participate in these reactions, and if so, whether they would react as carbon- or nitrogen-nucleophiles.

During preliminary optimization studies, they found that reaction conditions comparable to those used with other nucleophiles described above did lead to the conversion of **1-2** to the desired product **1-18** (**Table 1-1**). However, the results were highly irreproducible, and chemical yields varied widely from run-to-run when conducted in toluene at a 0.1 M reaction concentration. They reasoned that increasing the reaction concentration, or increasing the equivalents of indole added, may improve yields given the relatively poor nucleophilicity of indoles. But, further increasing the reaction concentration up to 1 M did not provide significantly better results, and separation of the excess indole from the product was difficult.

Table 1-1: Optimization of reactions with indole nucleophiles



1-2 **1-18**

Solvent	Temperature	Result
Toluene (0.1M to 1M)	95 °C	up to 62% yield, but irreproducible
None	95 °C	variable, irreproducible yields
Benzene (1M -> ~neat)	100 °C to 95 °C (solvent removed via distillation during initial reaction)	**66% yield, reproducible**

Ultimately, a key observation led to a solution of the reproducibility problem. In order to try to conduct as many reactions as possible in as short time period, the transformations were conducted in screw-capped vials in a metal heating block. Not every vial cap had a perfect seal, and in some instances the reaction solvent evaporated during the overnight run. Interestingly, the best results were obtained in the reactions where the solvent had evaporated.

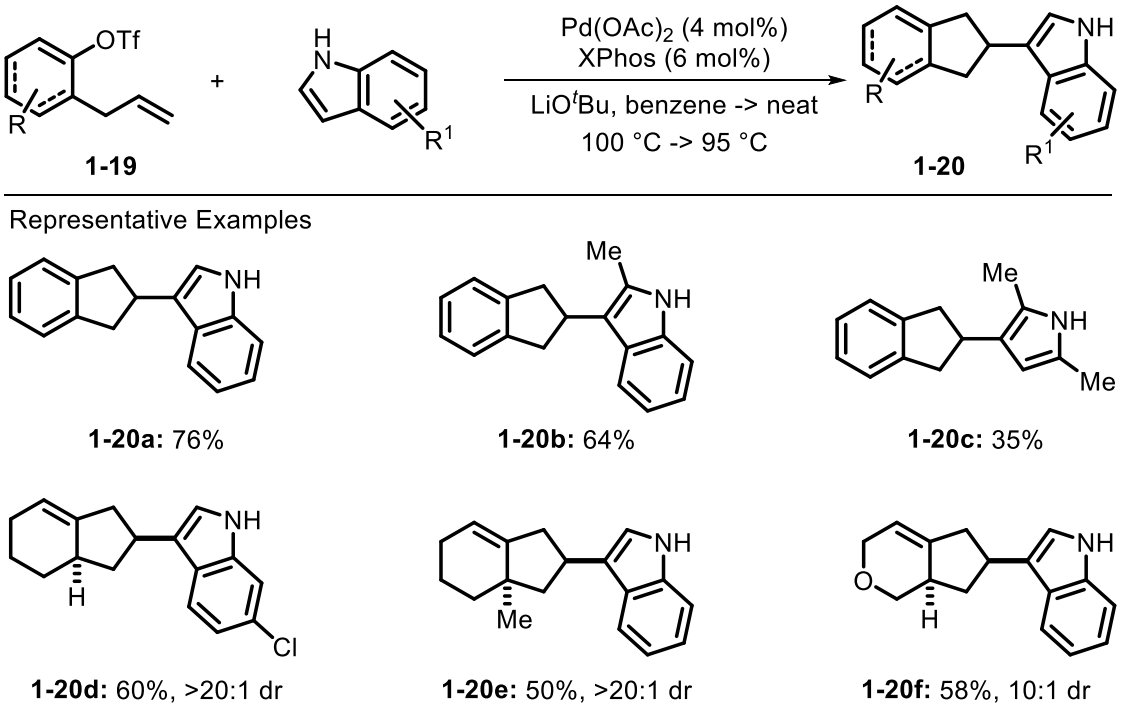
Dr. Kirsch reasoned that the extremely high concentration of indole present in the solvent-evaporated reaction mixtures was probably facilitating the transformations of these weak nucleophiles, and subsequently examined conducting reactions without solvent. Unfortunately, omitting solvent entirely also did not provide satisfactory reproducible yields.

It seemed that the lack of success with “neat” reaction conditions may be due to inefficient catalyst ligation/activation, since the only liquid present in the reaction mixture was the aryl triflate **1-2**. Based on this hypothesis, we devised a new reaction protocol, in which the reactions were set up using benzene as the solvent.[33] The reactions were conducted in round-bottom flasks equipped with a short-path distillation head, and after reagents were mixed, the reaction flask was heated to 100 °C and the benzene solvent was removed via distillation. The reaction temperature was then decreased slightly to 95 °C, and the reactions were allowed to stir for 3 h at this temperature in little or no solvent. These conditions proved to give satisfactory and reproducible yields.

As shown in **Scheme 1-14**, several different substituted indoles were suitable substrates. In all cases the indole alkylation occurred at C3 and competing N-alkylation was not observed. The presence of the indole N-H group was essential, as N-alkyl indoles

did not participate in the reaction. Unfortunately, efforts to extend this method to other heteroaromatic systems have thus far been unsuccessful. No reaction was observed with benzofuran or benzothiophene. The coupling of 2,5-dimethyl pyrrole did afford the desired product, but yields were modest due to oxidation of the electron-rich pyrrole product during the course of purification.

Scheme 1-14: Reactions of indole nucleophiles



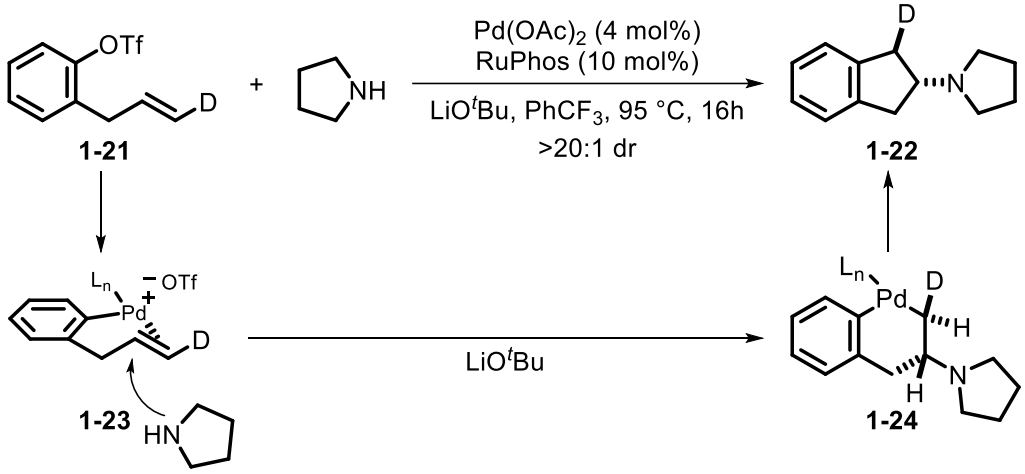
Both aryl and alkenyl triflates **1-19** were effective coupling partners, and products **1-20** were formed with good to excellent diastereoselectivity. However, the transformations were quite sensitive to steric properties of the substrate. Aryl triflates bearing substituted alkenes failed to react, and a substrate with a methyl group at the allylic position was transformed in low yield.

1.9 Mechanism and Stereochemistry of Palladium-Catalyzed Alkene Difunctionalization Reactions with Exogenous Nucleophiles

Dr. White's initial mechanistic hypothesis (**Section 1.3**, **Scheme 1-6**) suggested that the products of these reactions should result from net addition of the nucleophile and the

aryl (or alkenyl) group to the cyclizing double bond. In order to probe this hypothesis, Dr. White and co-workers examined the stereochemical outcome of the reaction between pyrrolidine and deuterated alkene substrate **1-21**.[26] As shown in **Scheme 1-15**, this reaction afforded *trans*-disubstituted product **1-22** as a single diastereomer (>20:1 dr). This result is consistent with our original hypothesis, involving oxidative addition to afford **1-23**, *anti*-aminopalladation of the alkene to give **1-24**, and then reductive elimination to provide the product **1-22**.

Scheme 1-15: Stereochemistry of alkene addition

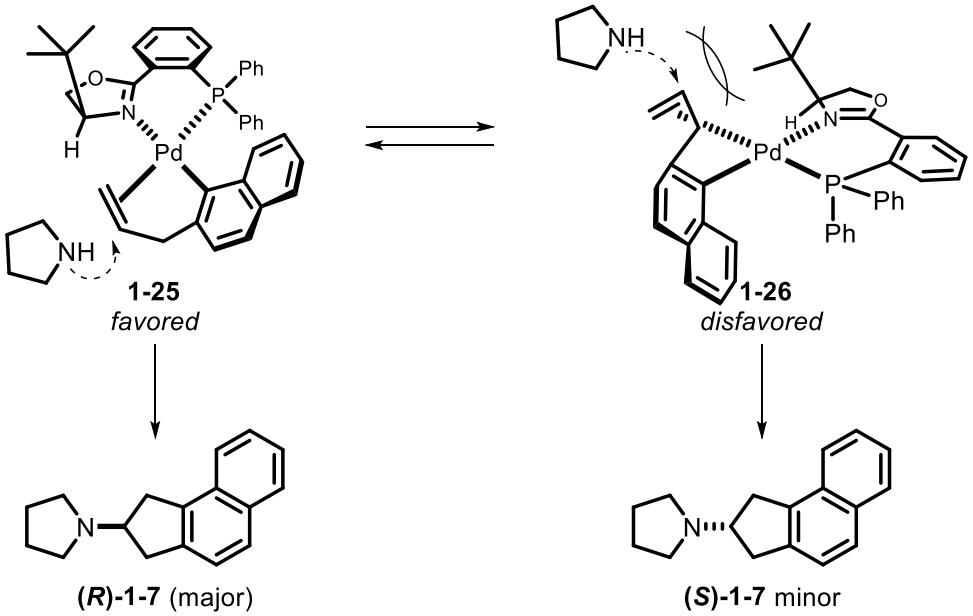


Our working model to explain both absolute and relative stereochemistry in these transformations is based on the mechanistic hypothesis derived above. We believe that the alkene hetero- or carbo-palladation step is likely the stereodetermining step of these reactions, but this step may be reversible depending on the nucleophile.[34] Our current stereochemical model does provide explanations for the origin of the major enantiomer or diastereomer in these transformations, but does not account for the influence of small changes to structure (sterics or electronics) on stereoselectivity.

Our working hypothesis for the origin of enantioselectivity in the Pd/*t*-butyl-phosphinooxazoline catalyzed reactions is based on a model originally proposed by Guiry for asymmetric Heck reactions.[35] As shown in **Scheme 1-16**,[26] following oxidative addition

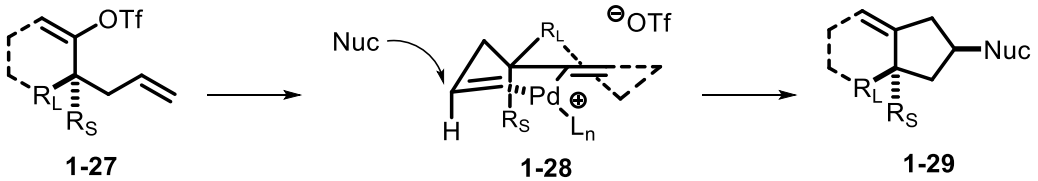
of the substrate, the alkene can bind to the metal such that the less-substituted carbon is relatively close to the bulky *tert*-butyl group (**1-25**), or with the more substituted and more hindered carbon of the alkene closer to the *tert*-butyl group (**1-26**, via rotation around the Pd-C_{Ar} bond axis). Reaction through the apparently less-sterically hindered and favored complex **1-25** leads to the observed major stereoisomer **(*R*)-1-7**.

Scheme 1-16: Model for enantioselectivity



We believe the relative stereochemistry in transformations of alkenyl triflate substrates is largely controlled by reaction through an organized, chair-like, transition state during the alkene nucleopalladation step of the catalytic cycle. As shown in **Scheme 1-17**, binding of the alkene through transition state **1-28**, in which the smaller group (R_S) is oriented in an axial position, would afford products with the observed relative stereochemistry between the nucleophile and the smaller substituent adjacent to the cyclizing allyl group. We cannot currently explain the influence of biaryl phosphine

Scheme 1-17: Model for diastereoselectivity



structure on stereocontrol that was observed in reactions of acyclic alkenyl triflates (**Scheme 1-11**), although it is possible that larger phosphines (e.g., BrettPhos) may result in reaction through pseudoaxial orientation of the cyclizing alkene.

1.10 Conclusion

In conclusion, the Wolfe group has developed a new class of alkene difunctionalization reactions between aryl or alkenyl triflates bearing tethered alkenes, and nucleophiles such as amines, alcohols, and indoles. The transformations generate two bonds, 1–2 stereocenters, and proceed in good yields and high diastereoselectivities for most cases. However, many important challenges remain unsolved, including the development of enantioselective variants of these reactions that have broad scope and generality. Many useful classes of nucleophiles have not yet been explored, and fully intermolecular reactions between an alkene, an aryl/alkenyl halide/triflate electrophile, and a nucleophile have not been developed. Chapter 2 will detail alkene difunctionalization reactions with enolate nucleophiles.

The work described in this chapter was published in the *Israel Journal of Chemistry*.[36] This chapter was adapted with permission from Bornowski, E. C.; Dr. White, D. R.; and Dr. Wolfe, J. P. *Isr. J. Chem.* **2020**, *60*, 259-267 Copyright (2020) John Wiley and Sons.

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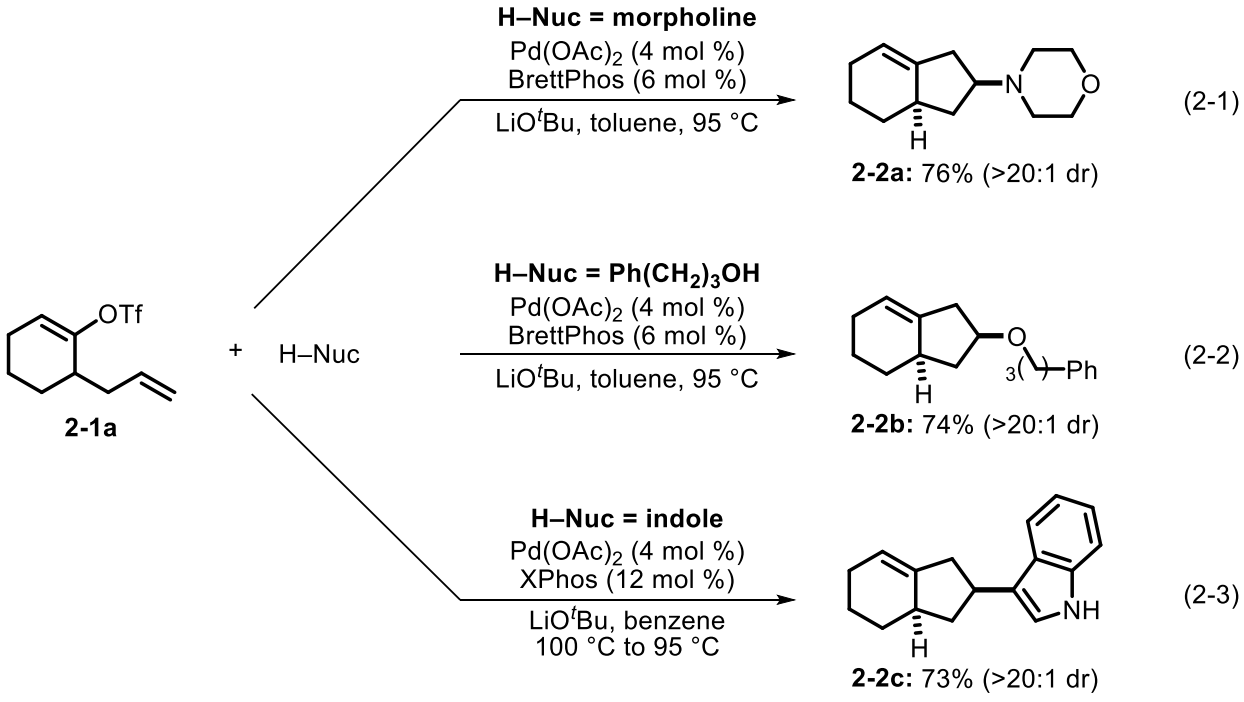
Chapter 2

Pd-Catalyzed Alkene Difunctionalization Reactions of Enolates for the Synthesis of Substituted Bicyclic Cyclopentanes

2.1 Introduction

In recent years, transition metal-catalyzed alkene difunctionalization reactions that form two carbon−carbon bonds have emerged as powerful tools for the construction of substituted alkanes, heterocycles, and carbocycles.[1,2] As described in Chapter 1, our group has described a new series of Pd-catalyzed alkene difunctionalization reactions that involve the coupling of amine,[3] alcohol/phenol,[4] or indole[5] nucleophiles with alkenes tethered to aryl or alkenyl triflates (**2-1a**). The transformations generate functionalized cyclopentane derivatives in good yield with high diastereoselectivity. For example, the Pd/BrettPhos-catalyzed coupling of **2-1a** with morpholine afforded **2-2a** in 76% yield with

Previous work

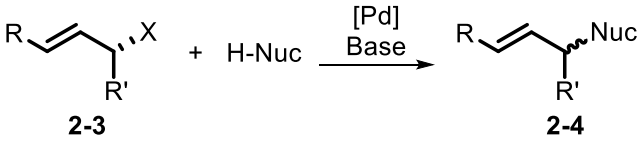


>20:1 dr (eq 2-1). Similarly, treatment of **2-1a** with 3-phenylpropanol (eq 2-2) or indole (eq 2-3) provided **2-2b** and **2-2c**, respectively, in good yields with >20:1 diastereoselectivity under appropriate conditions.

In order to further explore the scope of this general class of transformations, we elected to examine the use of stabilized carbanions as nucleophiles for alkene difunctionalization. We were cautiously optimistic about the chances for success at the outset of these studies, as enolates and related compounds have previously been employed as nucleophiles in a range of other palladium catalyzed reactions, including C-arylation[6] and allylic alkylation; most notably in the Tsuji-Trost reaction[7] (eq 2-4).

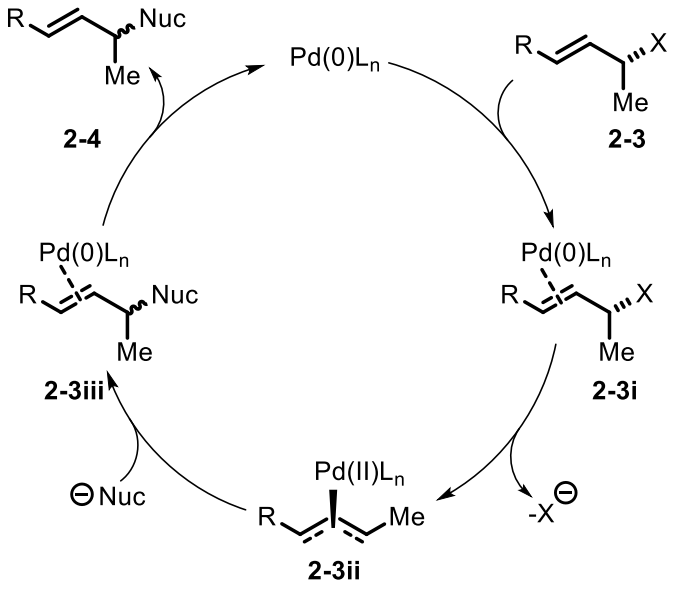
As shown in **Scheme 2-1**, the Tsuji-Trost reaction utilizes a substrate bearing an allylic leaving group (**2-3**) coordinating to form an η^2 π-allyl palladium(0) species (**2-3i**)

General Tsuji-Trost reaction[7]



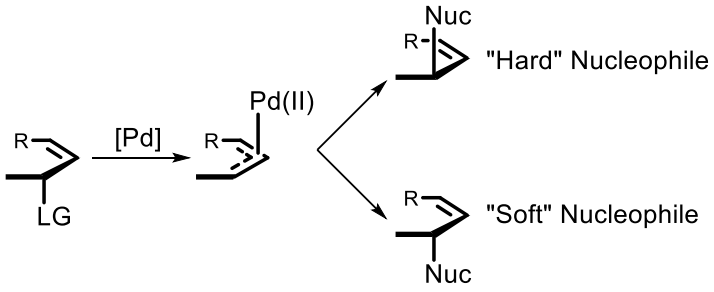
2-3 **2-4** (2-4)

Scheme 2-1: General Tsuji-Trost mechanism



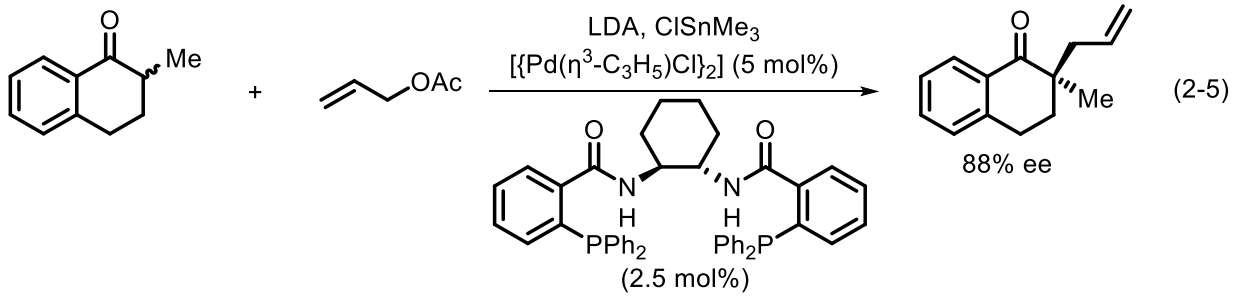
that undergoes oxidative addition forming an η^3 π-allyl palladium(II) complex (**2-3ii**). A nucleophile then adds to the allylic group, effectively allowing the η^3 π-allyl palladium (II) complex to undergo reductive elimination back to an η^2 π-allyl palladium (0) complex (**2-3iii**). The product (**2-4**) is liberated from the metal as the mechanistic cycle turns over.[8] The relative stereochemistry of the Tsuji-Trost reaction is determined by the "hardness" of the nucleophile (usually determined by the pk_a of the conjugate acid with pk_as < 25 categorized as "soft" and pk_as > 25 as "hard").[9] As shown in **Scheme 2-2**, a soft nucleophile will give overall retention of stereochemistry due the exogenous nucleophilic attack of the least substituted carbon of the coordinated η^3 complex. Hard nucleophiles

Scheme 2-2: General stereoselectivity of hard/soft nucleophiles in Tsuji-Trost reaction



give overall inversion of stereochemistry due to nucleophilic attack of the metal center and subsequent reductive elimination.[10] Typically, malonates are employed as soft nucleophiles in the Tsuji-Trost reaction and recently, harder stabilized enolates have been utilized as overall soft nucleophiles (eq 2-5).[7a]

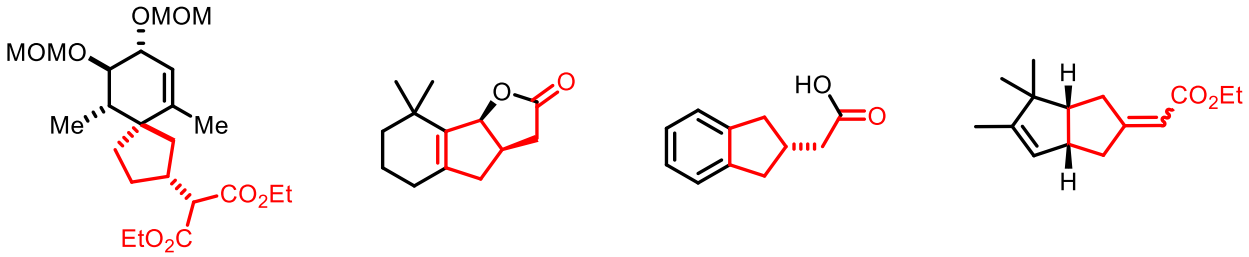
Braun 2007[7a]



(2-5)

With this in mind, we first sought to explore the use of malonates as carbon centered nucleophiles in alkene aryl-alkylation or alkenyl-alkylation variants of our previous transformations. Harder stabilized enolates were also hypothesized to be adequate exogenous nucleophiles in our difunctionalization reactions. In addition, cyclopentane derivatives bearing malonate, ester, or ketone groups have previously shown utility as synthetic intermediates (select examples shown in **Scheme 2-3**).[11,12] Importantly, the resulting carbonyl-substituted cyclopentane products could be further elaborated through manipulation of the carbonyl or functionalization of the double bond in alkenyl-triflate derived products. Therefore, the following describes a set of new alkene difunctionalization reactions of malonates, esters, and ketones that provide substituted cyclopentane derivatives in moderate to good yields with high levels of diastereoselectivity.

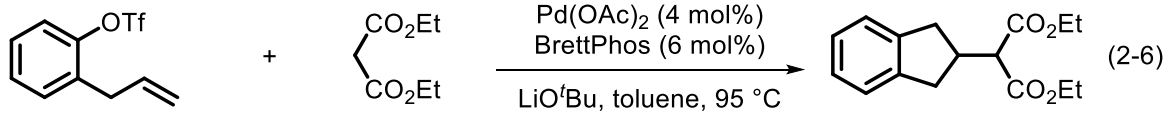
Scheme 2-3: Synthetic carbonyl functionalized cyclopentanyl intermediates for the synthesis of (from left to right) (±)-Oxylubimin, 5-Deoxystrigol, (+)-Salvileucalin B, Komarovispiranes



The work described in this chapter is comprised of both the author's (ECB), Derick R. White's (DRW), and Elsa M. Hinds' (EMH) contributions. DRW conducted early reaction optimization (eq 2-6, 0.2 mmol scale) and initial substrate scope investigations. EMH conducted reactions with internal olefins (**Scheme 2-4**: products **2-6e – 2-6h**; **Section 2.4**; **Section 2.5**) and synthesis of internal olefin starting materials. I have decided to include DRW's and EMH's results in this dissertation to give the reader the full story about this transformation.

2.2 Optimization of Reaction Conditions

In order to probe the feasibility of alkene difunctionalization reactions involving enolate nucleophiles, we initially examined the coupling of diethyl malonate with 2-allylphenyl triflate (**2-5a**). We began our studies using conditions we had previously developed for similar reactions of alcohol or amine nucleophiles and were pleased to find that these conditions provided satisfactory results in this transformation (eq 2-6). The desired product **2-6a** was formed in 93% isolated yield on a 0.2 mmol scale, 84% isolated yield on a 1.0 mmol scale, and 88% yield on a 1.5 g scale.



(2-6)

2-5a

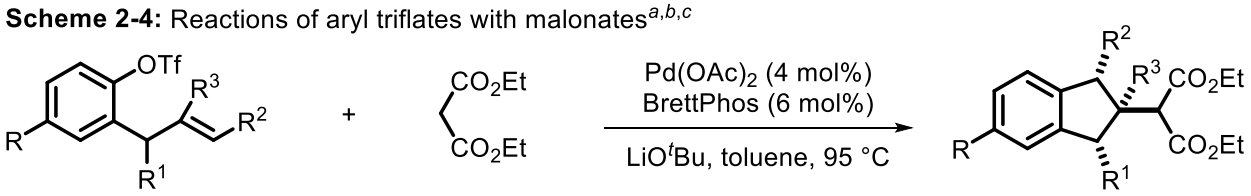
2-6a: 93% (0.2 mmol scale)
84% (1.0 mmol scale)
88% (1.5 gram scale)

2.3 Reaction Scope and Limitations of Aryl and Alkenyl Triflates with Malonates

Given the successful outcome of this initial reaction, we elected not to pursue further optimization of conditions but instead decided to explore the scope of this transformation (**Scheme 2-4**). Reactions between diethyl malonate and terminal alkene substrates (**2-5a–d**) proceeded in good yield under our standard reaction conditions, and substrate **2-5d** was converted to **2-6d** with >20:1 dr. In contrast, internal alkene substrates **2-5e–h** were less reactive and suffered from competing base-mediated isomerization of the alkene and/or cleavage of the triflate to give the corresponding phenoxide. However, these problems could be alleviated to some extent through use of increased amounts of diethyl malonate (3.6 equiv) and lithium tert-butoxide (2.2 equiv) combined with a lower reaction temperature of 65 °C. Under these modified conditions, products **2-6e−h** were obtained with >20:1 dr, albeit in modest isolated yields (33−46%).11 The diminished

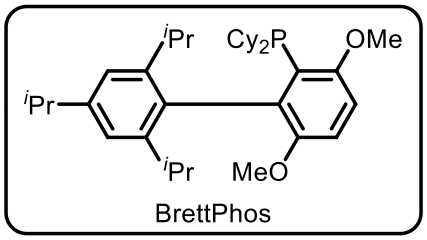
reactivity of the internal alkene substrates is presumably due to their increased steric bulk,

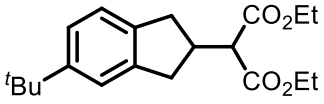
Scheme 2-4: Reactions of aryl triflates with malonates[a,b,c]



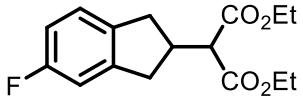
2-6b-i

2-5b: R = ^{t}Bu, R^1, R^2, R^3 = H
2-5c: R = F, R^1, R^2, R^3 = H
2-5d: R = H, R^1 = Me, R^2, R^3 = H
2-5e: R, R^1, R^3 = H, R^2 = Ph
2-5f: R = F, R^1, R^3 = H, R^2 = Ph
2-5g: R = OMe, R^1, R^3 = H, R^2 = Ph
2-5h: R = Me, R^1, R^3 = H, R^2 = Ph
2-5i: R = ^{t}Bu, R^1, R^2 = H, R^3 = Me

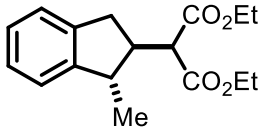




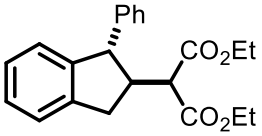
2-6b: 77%



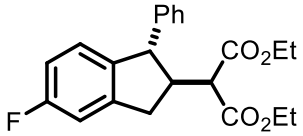
2-6c: 79%



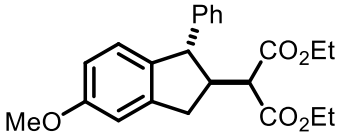
2-6d: 75%, >20:1 dr[d]



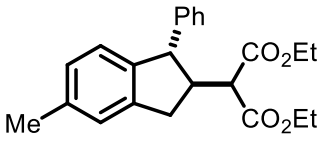
2-6e: 46%, >20:1 dr[e,f]



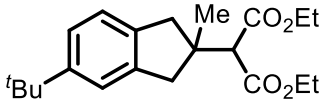
2-6f: 44%, >20:1 dr[e,f]



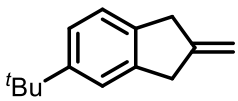
2-6g: 35%, >20:1 dr[e,f]



2-6h: 33%, >20:1 dr[e,f]



2-6i: 14%

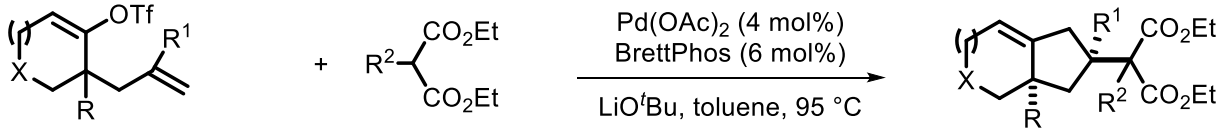


2-6i-a: 61%

[a]Conditions: 1.0 equiv of 5, 1.2 equiv of diethyl malonate, 1.4 equiv of LiO^{t}Bu, 4 mol% $Pd(OAc)_2$, 6 mol% BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1−0.25 mmol scale. [b]Diastereomeric ratios were determined by ^{1}H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. [c]Yields are average isolated yields of two or more experiments. [d]The reaction was conducted using (BrettPhos)Pd(allyl)(Cl) in place of $Pd(OAc)_2$. [e]The reaction was conducted using 2.2 equiv of LiO^{t}Bu and 3.6 equiv of diethyl malonate, a substrate concentration of 0.8 M, and a reaction temperature of 65 °C. [f]The reaction and isolation was conducted by Dr. Elsa Hinds.

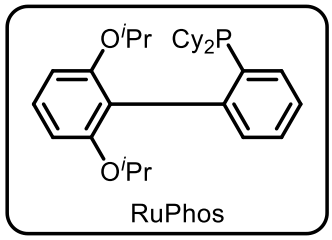
which decreases the facility by which the alkene is bound to palladium. Substrate **2-5i**, which contains a methyl group at the internal alkene carbon was transformed to **2-6i** in only 14% yield because of competing, and somewhat surprising, 5-endo Heck-type

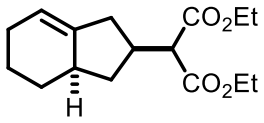
Scheme 2-5: Reactions of alkenyl triflates with malonates[a,b,c]



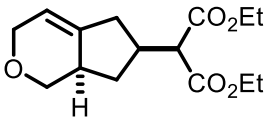
2-7a-g

2-1a: n = 1, X = CH_2, R, R^1 = H
2-1b: n = 1, X = O, R, R^1 = H
2-1c: n = 1, X = NBoc, R, R^1 = H
2-1d: n = 1, X = CH_2, R = H, R^1 = Me
2-1e: n = 0, X = CH_2, R = allyl, R^1 = H
2-1f: n = 0, X = CH_2, R = H, R^1 = Me
2-1g: n = 0, X = CH_2, R = CO_2Et, R^1 = Me

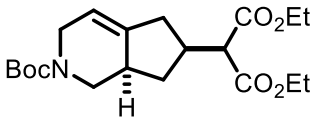




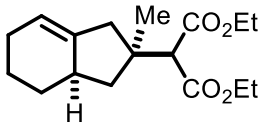
2-7a: 84%, >20:1 dr



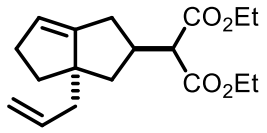
2-7b: 95%, >20:1 dr



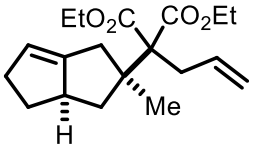
2-7c: 81%, >20:1 dr



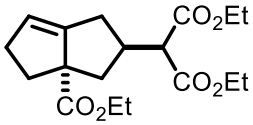
2-7d: 94%, 9:1 dr



2-7e: 92%, >20:1 dr



2-7f: 63%, 19:1 dr[d]



2-7g: 53%, >20:1 dr

[a]Conditions: 1.0 equiv of 1, 1.2 equiv of diethyl malonate, 1.4 equiv of LiO^{t}Bu, 4 mol% $Pd(OAc)_2$, 6 mol% BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1−0.25 mmol scale. [b]Diastereomeric ratios were determined by 1 H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. [c]Yields are average isolated yields of two or more experiments. [d]The reaction was conducted using RuPhos as the ligand.

cyclization of the substrate to yield **2-6i-a**. With longer reaction times, **2-6i-a** isomerized to the internal alkene.

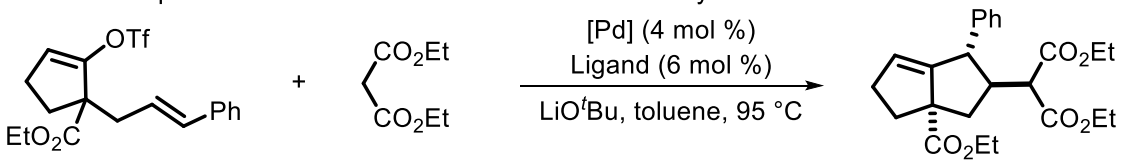
We subsequently turned our attention to cyclic alkenyl triflate substrates, which can be prepared from the corresponding cyclic ketones in two steps (Pd-catalyzed enolate allylation followed by formation of the enol triflate). Transformations of cyclic alkenyl triflates bearing pendent terminal alkenes proceeded in good to excellent yields in most cases examined (**Scheme 2-5**). The reactions were effective with substrates derived from both six and five-membered-ring ketones. Products bearing fused heterocyclic rings (**2-7b**, **2-7c**) were formed in good yields with high dr, and the presence of a substituent on the carbon bearing the allyl group (**2-7e**, **2-7g**) was tolerated. When coupling substrate **2-1d** with diethyl malonate, product **2-7d** was obtained in excellent yield, with moderate 9:1 dr, and smoothly providing a quaternary center at the functionalized carbon. The reaction between substrate **2-1f** and diethyl 2-allylmalonate provided **2-7f**, with the formation of a bond between two quaternary carbon atoms, in 63% yield with 19:1 dr, although use of the smaller RuPhos ligand was needed to obtain acceptable results.

2.4 Reoptimization of Reaction Conditions for Alkenyl Trfilates Bearing Internal Olefins

Efforts to couple alkenyl triflates bearing internal alkenes failed to provide satisfactory results either under these conditions (**Table 2-1**, entry 1), or under the re-optimized conditions that were modestly effective with aryl triflates. As such, Dr. Elsa Hinds elected to examine the influence of precatalyst and ligand structure on the reaction between diethyl malonate and **1l**. As shown in **Table 2-1**, use of other biaryl phosphines,[13] including CPhos, RuPhos, and SPhos that are less sterically hindered than BrettPhos provided improved results (45-48% yield). However, use of the wide bite angle ligand Dpe-Phos

afforded the desired product in 65% yield when LiHMDS was employed as base. We then examined $Pd(acac)_2$ as a precatalyst, as we have previously observed increased efficiency in other transformations when this precatalyst was used.[14] The combination of $Pd(acac)_2$ with SPhos provided the best results, affording **2-7p** in 79% yield and >20:1 dr.

Table 2-1: Optimization of reaction between **2-1l** and diethyl malonate[a,f]



2-1l **2-7p**

Entry	[Pd]	Ligand	Yield[b] (%)	dr[c]
1	$Pd(OAc)_2$	BrettPhos	5	>20:1
2	$Pd(OAc)_2$	CPhos	47	>20:1
3	$Pd(OAc)_2$	RuPhos	48	>20:1
4	$Pd(OAc)_2$	SPhos	45	>20:1
5	$Pd(OAc)_2$	dpe-Phos	65	>20:1[d]
6	$Pd(acac)_2$	dpe-Phos	47[e]	>20:1
7	$Pd(acac)_2$	SPhos	79	>20:1

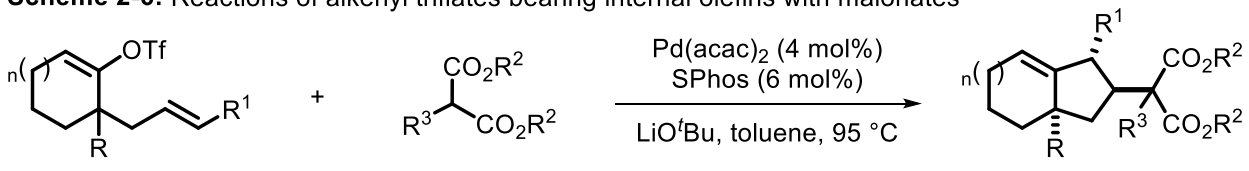
[a]Conditions: 1.0 equiv 1l, 2.0 equiv diethyl malonate, 4 mol% Pd, 6 mol% ligand, 2.2 equiv LiO^{t}Bu, toluene (0.8 M), 95 °C, 14 h. [b]Isolated yield (average of two or more experiments). [c]Diastereomeric ratios were determined by 1H NMR analysis. [d]LiHMDS was used as a base instead of LiO^{t}Bu. [e]The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using phenanthrene as an internal standard. [f]Reaction optimization was conducted by Dr. Elsa Hinds.

2.5 Reaction Scope and Limitations of Alkenyl Triflates Bearing Internal Olefins with Malonates

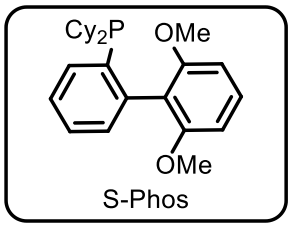
Dr. Elsa Hinds then examined the use of these newly optimized conditions with a number of different internal alkene substrates (**Scheme 2-6**). The transformations proceed in moderate to good yield, with generally high (>20:1) diastereoselectivity. A substituent (R ≠ H) on the carbon bearing the tethered alkene was tolerated, and in some

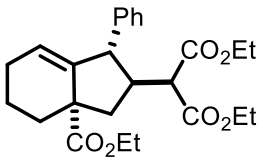
instances provided a significant increase in yield. For example, the coupling of **2-1l** (R =

Scheme 2-6: Reactions of alkenyl triflates bearing internal olefins with malonates[a,b,c,e]

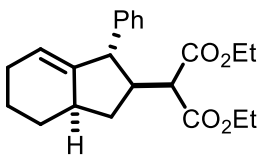


2-1h: n = 1, R = CO_2Et, R^1 = Ph
2-1i: n = 1, R = H, R^1 = Ph
2-1j: n = 1, R = CO_2Et, R^1 = Me
2-1k: n = 1, R = Me, R^1 = Ph
2-1l: n = 0, R = CO_2Et, R^1 = Ph
2-1m: n = 0, R = H, R^1 = Ph

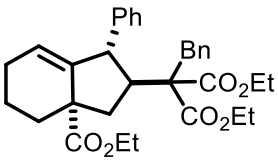




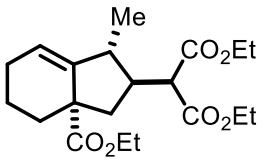
2-7h: 62%, >20:1 dr



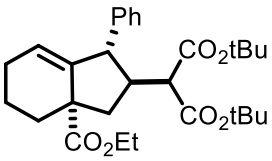
2-7i: 71%, >20:1 dr



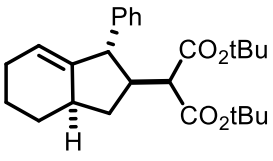
2-7j: 45%, >20:1 dr[d]



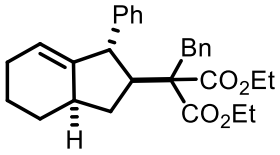
2-7k: 43%, >20:1 dr



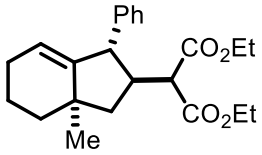
2-7l: 53%, >20:1 dr



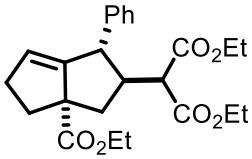
2-7m: 58%, >20:1 dr



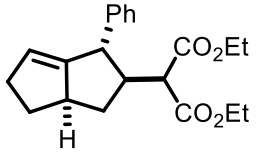
2-7n: 40%, >20:1 dr[d]



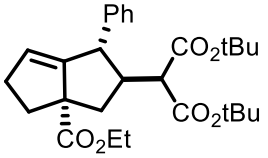
2-7o: 55%, >20:1 dr



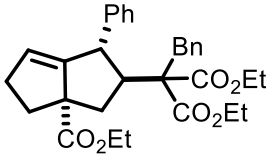
2-7p: 79%, >20:1 dr[d]



2-7q: 21%, >20:1 dr



2-7r: 55%, >20:1 dr



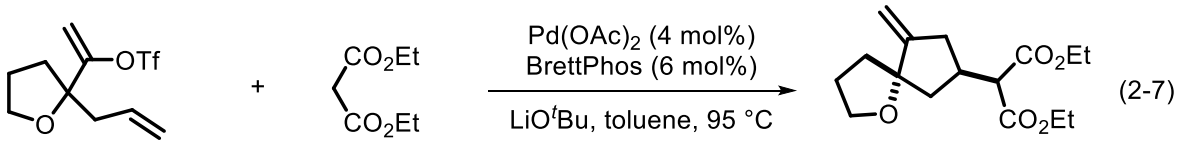
2-7s: 42%, >20:1 dr[d]

[a]Conditions: 1.0 equiv 1, 3.6 equiv diethyl malonate, 2.2 equiv LiO^{t}Bu, 4 mol% $Pd(acac)_2$, 6 mol% SPhos, toluene (0.8 M), 95 °C, 14 h. Reactions were conducted on a 0.2 mmol scale. [b]Diastereomeric ratios were determined by ^{1}H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. [c]Yields are average isolated yields of two or more experiments. [d]The reaction was conducted in xylenes solvent at 110 ° C. [e]Reactions and isolation of compounds preformed by Dr. Elsa Hinds.

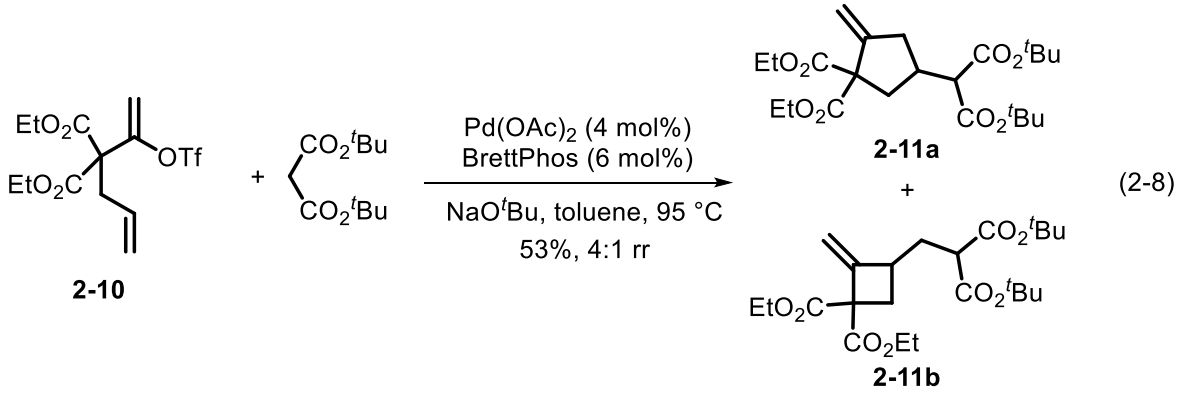
CO_2Et) with diethyl malonate proceeded to give **2-7p** in 79% yield, whereas the analogous substrate **2-1m** (R = H) was converted to **2-7q** in only 21% yield. Not surprisingly, use of di-*tert*-butyl malonate as the nucleophile provided results similar to those obtained with diethyl malonate. Transformations involving diethyl 2-benzyl malonate also provided desired products **2-7j**, **2-7n**, and **2-7s** in >20:1 dr, although higher reaction temperatures were required (110 °C), and chemical yields were lower than those obtained with the unsubstituted diethyl malonate nucleophile.

2.6 Reaction Scope and Limitations of Acyclic Alkenyl Triflates with Malonates

In prior studies involving amine or alcohol nucleophiles, we found that acyclic alkenyl triflates are also viable substrates in related alkene difunctionalization reactions.[3b,4] As such, we briefly examined the reactivity of two acyclic substrates with diethyl malonate. As shown in eq 2-7, the coupling of **2-8** with diethyl malonate proceeded smoothly under standard conditions to afford spirocycle **2-9** in 82% and >20:1 dr. However, when *gem*-diester substrate **2-10** was treated with di-*tert*-butyl malonate under analogous conditions,



2-8 **2-9**: 82%, >20:1 dr (2-7)



2-10 (2-8)

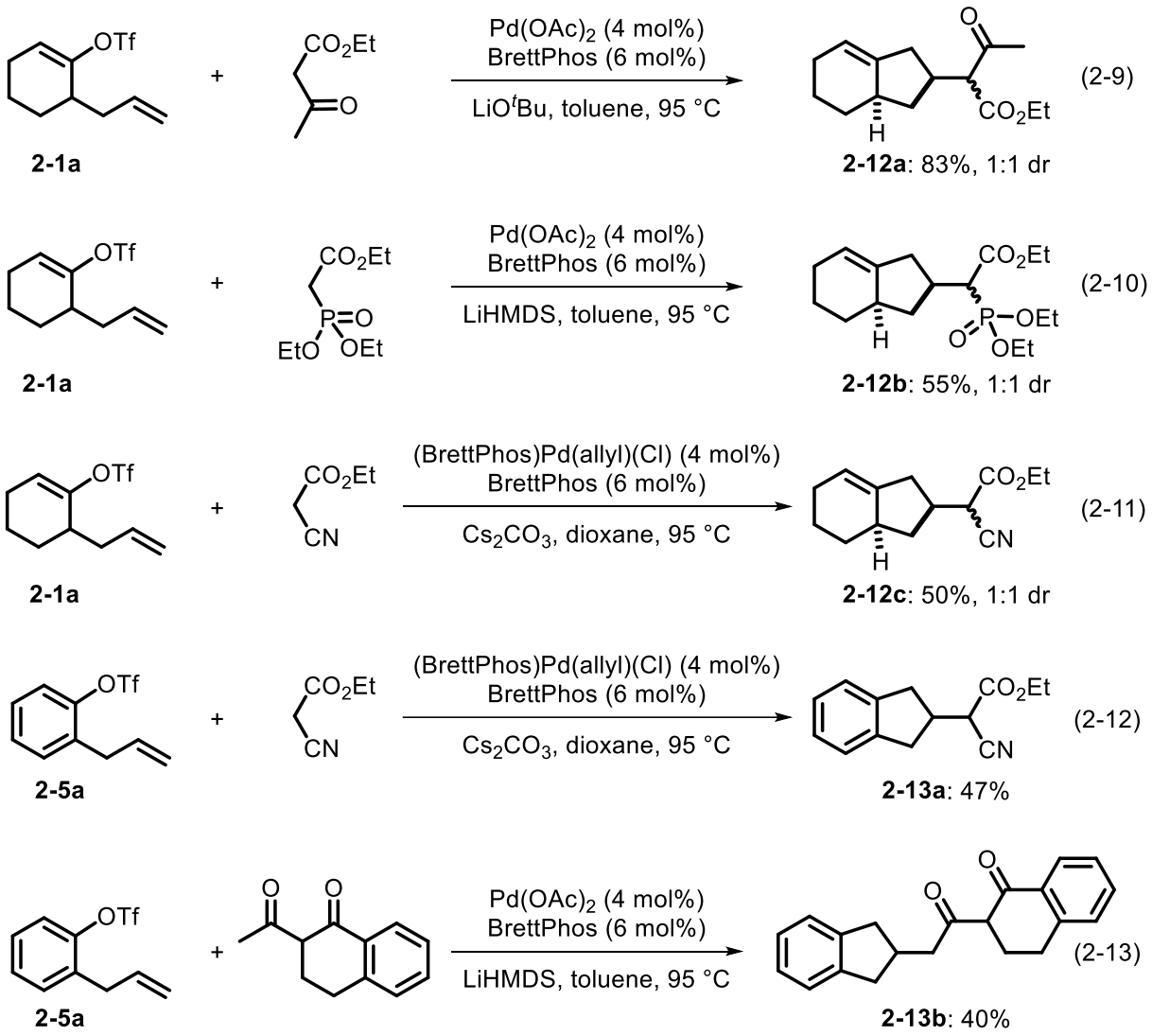
we obtained a 4:1 mixture of **2-11a**:**2-11b** in 53% yield (eq 2-8). A preliminary screen of several other phosphine ligands, including X-Phos, dpe-Phos, and P(2-furyl)$_3$, provided similar mixtures of **2-11a**:**2-11b** (ranging from 2:1 to 1:2.5) in good yields (up to 90% for the mixture). Chapter 3 is directed towards improving the regioselectivity in these transformations and exploring the scope of the reaction.

2.7 Reaction Scope and Limitations of Alkenyl and Aryl Triflates with Other Stabilized Carbanions

In addition to symmetrical malonate esters, these transformations are also effective with other stabilized carbanion nucleophiles. For example, the reaction between **2-1a** and ethyl acetoacetate afforded **2-12a** in 83% yield as a 1:1 mixture of stereoisomers epimeric at the stereocenter adjacent to the carbonyl group (**Scheme 2-7**, eq 2-9). Use of triethyl phosphonoacetate as the nucleophile, combined with LiHMDS as base, provided **2-12b** in 55% yield on a 1.85 mmol scale (**Scheme 2-7**, eq 2-10). However, reactions involving other activated nucleophiles were more challenging. Ethyl cyanoacetate was much less reactive than diethyl malonate, and only small amounts of desired product were formed under standard conditions. Nonetheless, after some experimentation we were able to produce **2-12c** in 50% yield by using (BrettPhos)Pd(allyl)Cl as the precatalyst[15] along with Cs_2CO_3 as base (**Scheme 2-7**, eq 2-11). These conditions were also effective for the coupling of 2-allylphenyl triflate **2-5a** with ethyl cyanoacetate to afford **2-13a** in 47% yield (**Scheme 2-7**, eq 2-12). Efforts to employ 2,4-pentanedione (acac) as the nucleophile provided only trace amounts of product, possibly due to inhibition of catalysis by acac acting as a ligand for Pd. In contrast, **2-5a** was successfully coupled with 2-acetyltetralone under modified conditions in which an excess (2.6 equiv) of LiHMDS was employed as base. In this case the alkylation occurred on the methyl group rather than the carbon

between the carbonyls, presumably via the dianion derived from 2-acetyltetralone, to afford **2-13b** (**Scheme 2-7**, eq 2-13) in 40% yield.[16] The modest yield results from competing arylation[6] of the methyl ketone with 2-allylphenyl triflate, rather than alkene difunctionalization. Although these other nucleophiles proved to be viable with terminal alkene substrates, efforts to couple them with internal alkene derivatives have thus far been unsuccessful.

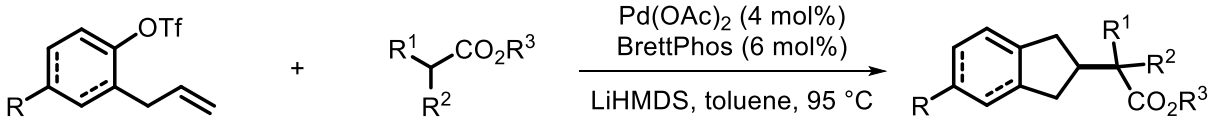
Scheme 2-7: Reactions of alkenyl and aryl triflates with stabilized carbanions



2.8 Reaction Scope and Limitations of Alkenyl and Aryl Triflates with Esters

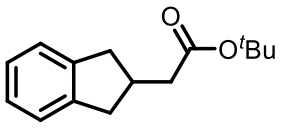
Given the successful transformations of malonates and related nucleophiles, we sought to further expand the scope of this method by employing other carbonyl-containing nucleophiles. As such, we surveyed the reactivity of a few aryl and alkenyl triflate substrates towards several different esters. Efforts to employ acetate esters gave poor results, as represented by the formation of **2-14a** in only 24% yield. The main side reaction

Scheme 2-8: Reactions of alkenyl and aryl triflates with esters[a,b,c]

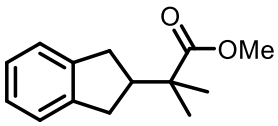


2-1a, 2-1d, **2-1f**, **2-5a, 2-5i**, or
2-5j (2-[2-methylallyl]-4-fluorophenyl triflate)

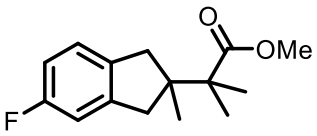
2-14a-h



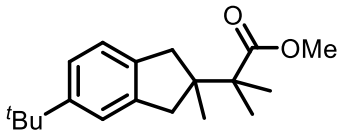
2-14a: 24%



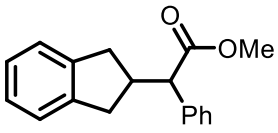
2-14b: 85%



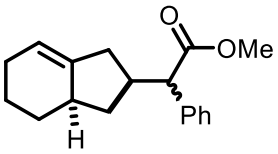
2-14c: 23%[d]



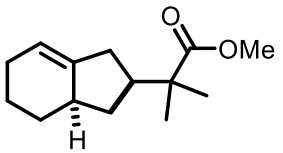
2-14d: 24%[d]



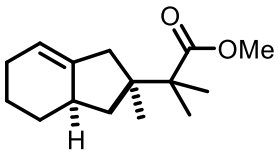
2-14e: 86%



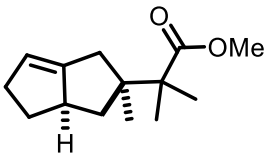
2-14f: 54%, 2:1 dr



2-14g: 88%, >20:1 dr



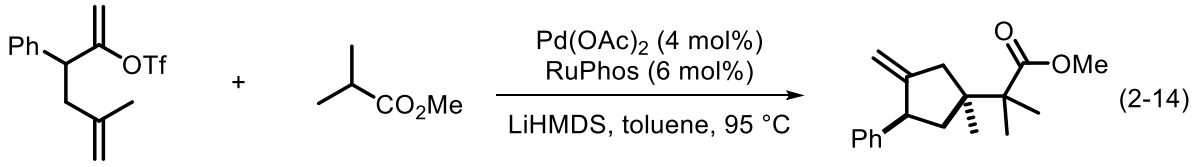
2-14h: 52%, 11:1 dr[d]



2-14i: 50%, >20:1 dr[d]

[a]Conditions: 1.0 equiv triflate substrate, 1.2 equiv ester, 2.2 equiv LiHMDS, 4 mol% $Pd(OAc)_2$, 6 mol% BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1-0.25 mmol scale. [b]Diastereomeric ratios were determined by ^{1}H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. [c]Yields are average isolated yields of two or more experiments. [d]RuPhos was used in place of BrettPhos as the ligand.

in this case is identical to that observed with 2-acetyltetralone – competing α-arylation of the ester with the aryl triflate substrate. In contrast, much better results were obtained with more highly substituted esters. For example, the sterically hindered methyl isobutyrate was coupled with terminal alkene substrates **2-5a** and **2-1a** to afford **2-14b** and **2-14g** in high yield. This hindered ester was also successfully coupled with substrates bearing a methyl group on the internal alkene carbon (**2-1d**, **2-1f**, **2-5i**, and **2-5j**) when RuPhos was used as the ligand for Pd. These reactions afforded **2-14h**, **2-14i**, **2-14d**, and **2-14c** in 52%, 50%, 24%, and 23% yield, respectively. Although the yields in these particular transformations are modest, the reactions do affect the formation of a C–C bond between two quaternary carbon atoms, and products **2-14h** and **2-14i**[17] were formed with high diastereoselectivity (11:1 dr and >20:1 dr, respectively). Acyclic alkenyl triflate **15** was also successfully coupled with methyl isobutyrate using the $Pd(OAc)_2$/RuPhos catalyst to afford **16** in 52% yield and >20:1 dr (eq 2-14). Reactions between **2-1a** or **2-5a** and methyl 2-phenyl acetate afforded **2-14e** and **2-14f** in moderate to good yield, but **2-14f** was obtained as a 2:1 mixture of diastereomers epimeric at the stereocenter adjacent to the ester.



(2-14)

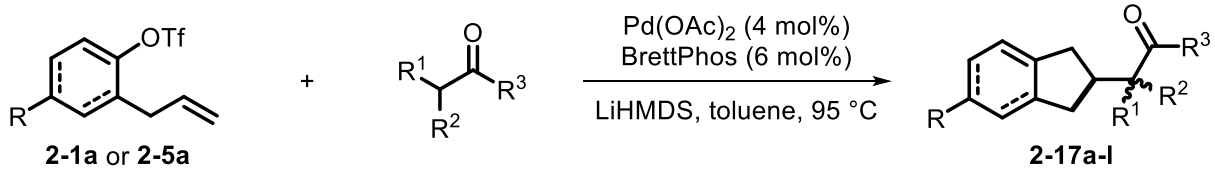
15 **16**: 52%, >20:1 dr

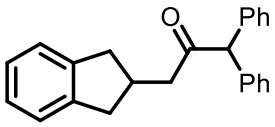
2.9 Reaction Scope and Limitations of Alkenyl and Aryl Triflates with Ketones

The coupling of **2-1a** or **2-5a** with several different ketones also proceeded smoothly, and this series of reactions exhibited the same general trends that were observed with ester nucleophiles. Low to moderate yields were obtained with methyl ketones (**2-17a**; 24% and **2-17h**; 52%), and in the case of 1,1-diphenyl acetone, reaction selectively

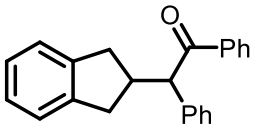
occurred at the less hindered carbon, rather than through the more highly substituted, thermodynamic enolate. However, reactions of several other ketones, including α-phenylacetophenone, α-tetralone, 6-methoxy-α-tetralone, and cyclohexanone, proceeded smoothly. In all cases examined, products were generated with essentially

Scheme 2-9: Reactions of alkenyl and aryl triflates with ketones[a,b,c]

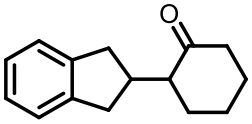




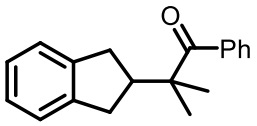
2-17a: 24%



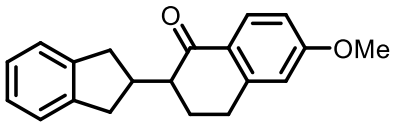
2-17b: 81%



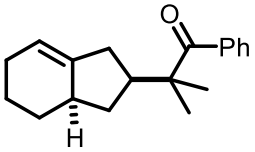
2-17c: 71%[d]



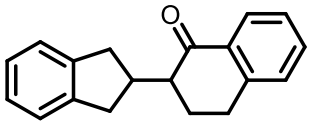
2-17d: 67%



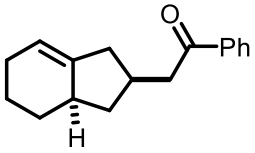
2-17e: 72%



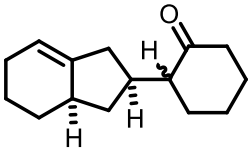
2-17f: 53%, >20:1 dr



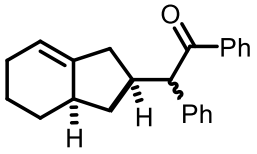
2-17g: 72%



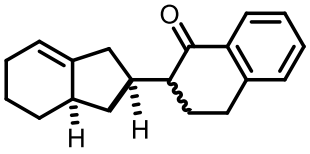
2-17h: 52%, >20:1 dr



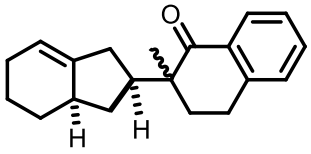
2-17i: 68%, 1:1 dr[d]



2-17j: 72%, 1:1 dr



2-17k: 79%, 1:1 dr



2-17l: 56%, 1:1 dr

[a]Conditions: 1.0 equiv triflate substrate, 1.2 equiv ketone, 1.4 equiv LiHMDS, 4 mol% $Pd(OAc)_2$, 6 mol% BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1-0.25 mmol scale. [b]Diastereomeric ratios were determined by ^1H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. [c]Yields are average isolated yields of two or more experiments. [d]The reaction was conducted with 2.6 equiv of the ketone.

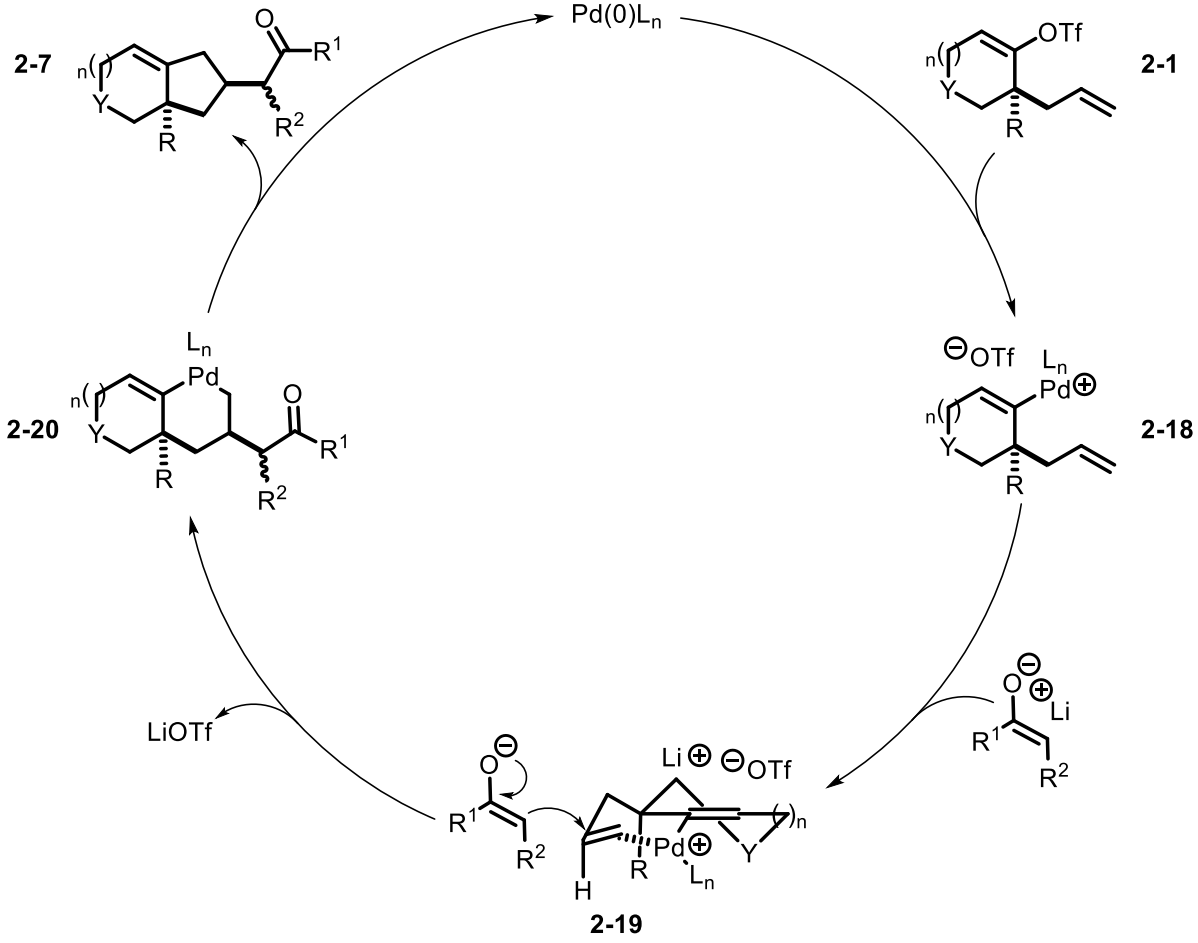
complete control of relative stereochemistry around the bicyclic ring system. Products **2-17i**, **2-17j**, and **2-17k**, which contain a base-epimerizable stereocenter, were formed as essentially 1:1 mixtures of diastereomers epimeric at the carbonyl-bearing stereocenter. However, the reaction of 2-methyl-α-tetralone to produce **2-17l**, which lacks a base-epimerizable proton, also proceeded with 1:1 dr. Interestingly, cyclohexanone underwent selective monoalkylation (using 2.6 equiv of cyclohexanone) to provide **2-17c** and **2-17i**; bis-alkylation products were not observed. This is likely due to the use of excess cyclohexanone, along with the fact that the thermodynamic enolates derived from products **2-17c** and **2-17i** are sterically encumbered. These hindered enolates should react much more slowly than the enolate of cyclohexanone itself, and the less-substituted "kinetic" enolates of the monoalkylated cyclohexanone products should be present in relatively low concentration under these conditions.

2.10 Mechanism and Stereochemical Model

Based on the stereochemical outcome of transformations involving internal alkenes, in which products result from *anti*-addition of the nucleophile and the aryl or alkenyl group to the pendant alkene, the mechanism of these transformations is probably similar to those of related reactions of amine, alcohol, or indole nucleophiles.[3,4,5] As illustrated in **Scheme 2-10**, the reactions are likely initiated by oxidative addition of the aryl or alkenyl triflate (**2-1**) to a Pd(0) complex generated by ligation and reduction of the Pd(II) precatalyst. After oxidative addition, the alkene in intermediate **2-18** is poised to bind to the Pd(II) center, which activates it for attack by the exogenous nucleophile in intermediate **2-19.** This intermediate then undergoes *anti*-carbopalladation to provide **2-20**, which is transformed to the desired product with regeneration of the Pd(0) catalyst

through reductive elimination. The observed major product stereochemistry is consistent with carbopalladation through a chair-like conformation in which non-bonding interactions are minimized. Although control of relative stereochemistry of the substituents on the bicyclic ring system is generally quite high, we currently are unable to control the relative stereochemistry of stereocenters adjacent to the carbonyl of the nucleophilic component. For products such as **2-14f** and **2-17i-k**, which contain an acidic proton at the carbonyl α-stereocenter, the poor stereocontrol is easily ascribed to epimerization under the strongly basic reaction conditions. However, the poor selectivity in the formation of **2-17l**, which does not contain an epimerizable α-stereocenter, reveals a second problem in

Scheme 2-10: Mechanism and relative stereochemistry



stereocontrol. In this case the 1:1 dr must result from inherently low relative face selectivity when the enolate approaches intermediate **2-19** (**Scheme 2-10**).

2.11 Conclusion

In conclusion, we have developed a series of new alkene difunctionalization reactions between alkenes bearing pendant aryl or alkenyl triflates, and enolate nucleophiles derived from esters, ketones, and malonates. Reactions of terminal alkene substrates are reasonably general, and transformations involving internal alkenes provide moderate yields when malonate nucleophiles are used. The reactions generate a ring and two C–C bonds, and provide products that contain up to three stereocenters with high diastereoselectivity in most cases examined. The product stereochemistry implicates a mechanism involving *anti*-carbopalladation of the alkene, which occurs with high diastereoselectivity. The transformations afford several different fused-bicyclic products, including heterocycles, although reactions that generate simple monocyclic cyclopentane derivatives are currently limited in scope due to the formation of regioisomeric cyclobutene products.

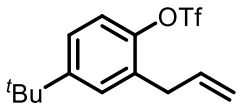
The work described in this chapter was published in *Organic Letters*[18] and *Organic Process Research & Development*.[19] This chapter was adapted with permission from Bornowski, E. C.; Dr. Hinds, E. M.; Dr. White, D. R.; Nakamura, Y.; and Dr. Wolfe, J. P. *Org. Lett.* **2019**, *21*, 3813–3816 Copyright (2019) American Chemical Society and *Org. Process Res. Dev.* **2019**, *23*, 1610–1630 Copyright (2019) American Chemical Society.

2.12 Experimental

General Considerations: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The

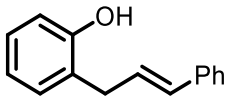
substrates **2-1a-e**,[3b] **2-1f**,[4] **2-1g**,[3a] **2-5a**,[3a] **2-5c**,[3a] **2-5d**,[3b] **2-8**,3[b] **2-10**,[3b] **2-15**,[3b] (Brettphos)Pd(allyl)(Cl),[15] *N*-(2-pyridyl)triflimide,[20] 4-*tert*-butyl-2-allylphenol,[21] and ally 1-methyl-2-oxocyclohexane-1-carboxylate[22] were prepared by previously published methods. Alkenyl triflate starting materials were stored in a freezer under nitrogen. Bulk quantities of cesium carbonate, lithium *tert*-butoxide, and lithium hexamethyldisilazide were stored in nitrogen-filled glove box, and small amounts were removed and used within a few days, during which time they were stored in a desiccator. Toluene, tetrahydrofuran, dichloromethane, and diethyl ether were purified using a GlassContour solvent purification system. Anhydrous 1,4 dioxane was purchased from Sigma-Aldrich and was used without purification. Structural and stereochemical assignments were made on the basis of 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in **Schemes 2-4** – **2-10** and equations 2-6 – 2-14 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in **Schemes 2-4** – **2-10** and equations 2-6 – 2-14.

Preparation and Characterization of Substrates



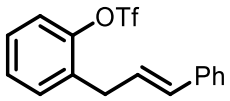
2-Allyl-4-(tert-butyl)phenyl trifluoromethanesulfonate (2-5b). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 2-allyl-4-*tert*-butylphenol (0.231 g, 1.21 mmol, 1.0 equiv) and dichloromethane (1.3 mL, 1 M).

Pyridine (0.117 mL, 1.48 mmol, 1.2 equiv) was added, and the reaction was cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.225 mL, 1.34 mmol, 1.1 equiv) was added, the ice bath was removed, and the reaction was stirred for 15 h at rt. The mixture was quenched with ammonium chloride and extracted with DCM (x3). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to yield a brown oil. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. This procedure afforded 0.334 g (85%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.19 – 7.14 (m, 1H), 5.98 – 5.87 (m, 1H), 5.18 – 5.09 (m, 2H), 3.47 (d, J = 6.6 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 145.7, 134.9, 131.9, 128.3, 125.1, 120.7, 118.5 (q, $J_{C\text{-}F}$ = 321 Hz) 117.2, 77.2, 34.7, 34.3, 31.2. IR (film) 2967, 1491 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{14}H_{17}F_3O_3S$ 323.0850; found 323.0565



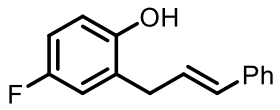
2-Cinnamylphenol (2-S1). A flame-dried 2-neck flask equipped with a stir bar and a condenser was cooled under a stream of nitrogen and charged with phenol (2.0 g, 21.2 mmol, 1.0 equiv) and diethyl ether (22 mL, 0.1 M). Sodium hydride (60% in mineral oil, 1.7 g, 42.4 mmol, 2.0 equiv) was added, and the reaction stirred at rt for 30 min. Cinnamyl chloride was added and the reaction heated to 37 °C with stirring for 6 h. The reaction was cooled to rt, and the mixture was transferred to an Erlenmeyer flask containing aqueous HCl (0.1 M, 75 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil. The crude material

was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 2.52 g (57%) of the title compound as a yellow semisolid, mp 57-58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 18.1 Hz, 4H), 7.25 – 7.11 (m, 3H), 6.91 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.44 – 6.34 (m, 1H), 4.89 (s, 1H), 3.58 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 137.1, 131.5, 130.5, 128.5 (2 peaks), 127.9 (2 peaks), 127.3, 126.2, 121.0, 115.8, 34.1. IR (film) 3531.5, 1591.7, cm^{-1}. HRMS (ESI^- TOF) m/z: $[M - H^+]^-$ calcd for $C_{15}H_{14}O$ 209.0966; found 209.0972.

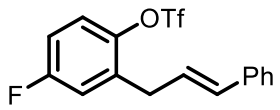


2-Cinnamylphenyl trifluoromethanesulfonate (2-5e). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 2-cinnamylphenol (**2-S1**) (0.934 g, 4.45 mmol, 1.0 equiv) and dichloromethane (20 mL, 0.2 M). Pyridine (0.72 mL, 8.9 mmol, 2.0 equiv) was added, and the reaction was cooled to 0 °C. Trifluoromethanesulfonic anhydride (1.5 mL, 8.9 mmol, 2.0 equiv) was added, the ice bath was removed, and the reaction was stirred for 15 h at rt. The purple mixture was filtered through a pad of celite, eluting with ethyl acetate. The purple filtrate was concentrated *in vacuo* to yield a purple oil. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 1.18 g (78%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.13 (m, 9H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.35 – 6.22 (m, 1H), 3.65 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 137.0, 133.1, 132.7, 131.4, 128.5, 128.2, 127.4, 126.2, 126.1,

121.4, 118.5 (q, $J_{C\text{-}F}$ = 319 Hz), 33.2, 29.7. IR (film) 1595.3, cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{16}H_{13}F_3O_3S$ 342.0538; found 342.0538.

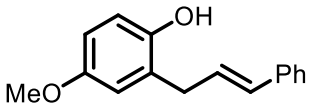


2-Cinnamyl-4-fluorophenol (2-S2). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenol (**2-S1**), except using 4-fluorophenol (2.9 g, 17.86 mmol, 1.0 equiv), cinnamyl chloride (2.5 mL, 17.86 mmol, 1.0 equiv), and sodium hydride (60% in mineral oil, 1.428 g, 35.7 mmol, 2.0 equiv). The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 2.617 g (64%) of the title compound as a yellow solid, mp 51-52 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 5H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 13.6 Hz, 1H), 6.75 (d, *J* = 13.4 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.78 (s, 1H), 3.54 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 156.2, 149.8 (d, *J* = 2.5 Hz), 136.9, 132.0, 128.6, 127.4 (d, *J* = 7.5 Hz), 127.0, 126.2, 116.6 (d, *J* = 31 Hz), 116.5 (d, *J* = 18 Hz), 113.9 (d, *J* = 23 Hz), 34.0. IR (film) 3411.7, 1619.3 cm^{-1}. HRMS (ESI^- TOF) m/z: $[M - H^+]^-$ calcd for $C_{15}H_{13}FO$ 227.0872; found 227.0878.

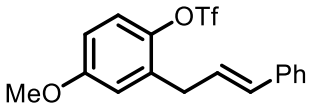


2-Cinnamyl-4-fluorophenyl trifluoromethanesulfonate (2-5f). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenyl trifluoromethanesulfonate (**2-5e**), except using 2-cinnamyl-4-fluorophenol (**2-S2**) (0.79 g, 3.47 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride

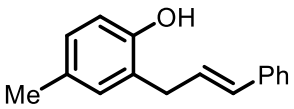
(1.16 mL, 6.94 mmol, 2.0 equiv), and pyridine (0.56 mL, 6.94 mmol, 2.0 equiv). The crude material was purified via column chromatography on silica gel using 100:1 -> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 0.8474 g (68%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.22 (m, 6H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.31 (dd, *J* = 15.8, 7.0 Hz, 1H), 3.69 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 160.6, 143.5 (d, *J* = 4 Hz), 136.8, 135.9 (d, *J* = 8 Hz), 133.5, 127.7, 126.3, 125.1, 123.1 (d, *J* = 9 Hz), 118.7 (q, *J* = 319 Hz), 117.9 (d, *J* = 24 Hz), 115.0 (d, *J* = 24 Hz), 33.3. IR (film) 1592.3, cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{16}H_{12}F_4O_3S$ 361.0522; found 361.0516.



2-Cinnamyl-4-methoxyphenol (2-S3). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenol (**2-S1**), except using 4-methoxyphenol (1.9 g, 14.4 mmol, 1.0 equiv), cinnamyl chloride (2.0 mL, 14.4 mmol, 1.0 equiv), and sodium hydride (60% in mineral oil, 1.15 g, 28.8 mmol, 2.0 equiv)). The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 1.516 g (44%) of the title compound as an orange solid, mp 74–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.10 (m, 5H), 6.83 – 6.61 (m, 3H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 4.59 (s, 1H), 3.76 (s, 3H), 3.54 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 137.0, 131.6, 128.6 (2 peaks), 128.5, 127.7, 126.8, 126.2, 116.5, 116.0, 112.6, 55.7, 34.3. IR (film) 3384.8, 1598.5, cm^{-1}. HRMS (ESI^{-} TOF) m/z: $[M - H^{+}]^{-}$ calcd for $C_{16}H_{16}O_2$ 239.1072; found 239.1078.

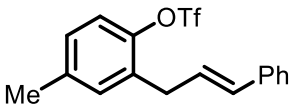


2-Cinnamyl-4-methoxyphenyl trifluoromethanesulfonate (2-5g). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenyl trifluoromethanesulfonate (**2-5e**), except using 2-cinnamyl-4-methoxyphenol (**2-S3**) (1.0 g, 4.17 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (1.4 mL, 8.33 mmol, 2.0 equiv), and pyridine (0.67 mL, 8.33 mmol, 2.0 equiv). The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 1.18 g (76%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.13 (m, 6H), 6.87 (s, 1H), 6.79 (d, J = 9.0 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 6.34 – 6.18 (m, 1H), 3.80 (s, 3H), 3.60 (d, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 141.3, 137.0, 134.4, 132.8, 128.5, 127.4, 126.2, 126.0, 122.4, 118.7 (q, $J_{C\text{-}F}$ = 305 Hz), 116.3, 112.8, 55.7, 33.5. IR (film) 1587.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + NH_4^+]$^+$ calcd for $C_{17}H_{15}F_3O_4S$ 390.0987; found 390.0981.

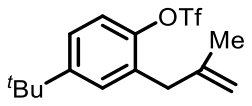


2-Cinnamyl-4-methylphenol (2-S4). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenol (**2-S1**), except using 4-methylphenol (2.3 mL, 22.0 mmol, 1.0 equiv), cinnamyl chloride (3.0 mL, 22.0 mmol, 1.0 equiv), and sodium hydride (60% in mineral oil, 1.80 g, 44.0 mmol, 2.0 equiv). The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 2.68 g (54%) of the title

compound as a yellow wax. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.14 (m, 5H), 7.04 – 6.88 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.56 – 6.46 (m, 1H), 6.44 – 6.33 (m, 1H), 4.75 (s, 1H), 3.54 (dd, *J* = 6.5, 1.4 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 137.1, 131.4, 131.0, 130.2, 128.5, 128.2, 128.1, 127.3, 126.2, 125.4, 115.6, 34.1, 20.5. IR (film) 3214.4, 2750.3, 1495.7, 1405.2, 1275.7 cm^{-1}. HRMS (Electron Impact Ionization TOF) m/z: $[M + H^+]^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1201.



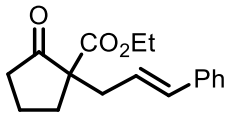
2-Cinnamyl-4-methylphenyl trifluoromethanesulfonate (2-5h). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylphenyl trifluoromethanesulfonate (**2-5e**), except using 2-cinnamyl-4-methylphenol (**2-S4**) (1.02 g, 4.46 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (1.5 mL, 8.93 mmol, 2.0 equiv), and pyridine (0.72 mL, 8.93 mmol, 2.0 equiv). The crude material was purified via column chromatography on silica gel using 100:0 -> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 1.20 g (76%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.20 (m, 1H), 7.20 – 7.13 (m, 2H), 7.10 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.35 – 6.21 (m, 1H), 3.61 (dd, *J* = 7.0, 1.5 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8, 138.5, 137.1, 132.6, 132.5, 131.9, 128.7, 128.5, 128.4, 127.4, 126.3, 118.6 (q, $J_{C\text{-}F}$ = 321 Hz), 121.1, 33.2, 20.9. IR (film) 3028.5, 2924.4, 1599.3, 1490.7, 1417.7 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + NH_4^+]^+$ calcd for $C_{17}H_{15}F_3O_3S$ 374.1038; found 374.1032.



4-(*tert*-Butyl)-2-(2-methylallyl)phenyl trifluoromethanesulfonate (2-5i). A flame-dried thick-walled sealable glass pressure flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 1-(*tert*-butyl)-4-[(2-methylallyl)oxy]benzene (5.33g, 26 mmol) and dimethylformamide (5 mL, 5.2 M). The solution was heated to 200°C for 12 h, then was cooled to rt and ethyl acetate (20 mL) was added. The mixture was transferred to a separatory funnel, washed with water (3 x 20 mL), then was dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a brown oil. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 4.05 g (76%) of 4-(tert-butyl)-2-(2-methylallyl)phenol as a colorless oil with ca 3% of a side product resulting from isomerization of the alkene. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.83 (s, 1H), 3.36 (s, 2H), 1.74 (s, 3H), 1.28 (s, 9H).

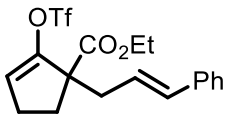
A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 4-(*tert*-butyl)-2-(2-methylallyl)phenol (1.4 g, 6.85 mmol, 1.0 equiv) and dichloromethane (7 mL, 1 M). Pyridine (1.4 mL, 8.22 mmol, 1.2 equiv) was added, and the mixture was cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.7 mL, 8.22 mmol, 1.2 equiv) was added, the ice bath was removed, and the reaction was stirred at rt for 15 h. The mixture was quenched with saturated aqueous ammonium chloride (10 mL) and then transferred to a separatory funnel. The mixture was extracted with dichloromethane (3 x 10 mL), then the organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated *in vacuo* to yield a brown oil. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. This procedure afforded 2.06 g (89%) of the title compound as a colorless oil that contained ca 6% of a side product resulting from alkene isomerization. Data are for the major

isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.20 – 7.14 (m, 1H), 4.89 (s, 1H), 4.66 (s, 1H), 3.40 (s, 2H), 1.72 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.34, 146.09, 142.74, 131.42, 128.76, 125.07, 120.58, 118.5 (q, $J_{C\text{-}F}$ = 321 Hz), 113.05, 38.29, 34.63, 31.23, 22.22. IR (film) 2951, 2700, 1480, 1415, 1208, 729 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{15}H_{19}F_3O_3S$ 337.1080; found 337.1077.



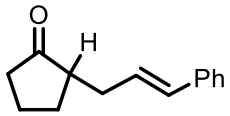
Ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (2-S5). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with sodium hydride (60% in mineral oil, 0.534 g, 13.35 mmol, 0.89 equiv) and THF (6 mL). The mixture was cooled to 0 °C and a solution of ethyl-2-oxocyclopentanecarboxylate (1.9 mL, 15 mmol, 1 equiv) in THF (10 mL) was added dropwise over the course of 90 min. The reaction mixture was warmed to rt and stirred for 90 min, then a solution of cinnamyl bromide (2.6 mL, 17.25 mmol, 1.15 equiv) in THF (5 mL) was added and the mixture was stirred at rt for 16 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. The crude material was purified via column chromatography on silica gel using 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 1.84 g (45%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 4H), 7.21 (d, *J* = 14.2 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.16 – 6.01 (m, 1H), 4.25 – 4.10 (m, 2H), 2.89 – 2.73 (m, 1H), 2.59 – 2.37 (m, 3H), 2.31 – 2.16 (m, 1H), 2.04 (d, *J* = 14.0 Hz, 2H), 1.90 (d, *J* = 17.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz,

3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6, 170.9, 137.0, 134.1, 128.5, 127.4, 126.2, 124.5, 61.5, 60.2, 38.1, 37.0, 32.3, 19.6, 14.1. IR (film) 1750.4, 1719.9, 1448.4 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{20}O_3$ 272.1413; found 273.1485.



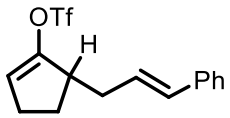
Ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (2-1l). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with THF (10 mL) and diisopropylamine (1.0 mL, 7.29 mmol, 1.7 equiv). The mixture was cooled to 0 °C, n-BuLi (2.5 M in hexanes, 2.9 mL, 7.29 mmol, 1.7 equiv) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. The mixture was cooled to -78 °C and a solution of ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (**2-S5**, 1.17 g, 4.29 mmol, 1 equiv) in THF (10 mL) was added dropwise over the course of 90 min. The reaction mixture was stirred at -78 °C for 2.5 h, then N-(2-pyridyl)triflamide (2.61 g, 7.29 mmol, 1.7 equiv) in THF (5 mL) was added and the mixture was warmed to rt and stirred for 16 h. The reaction was quenched with water (20 mL) and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 1.18 g (68%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.14 (m, 5H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.14 – 6.00 (m, 1H), 5.80 (s, 1H), 4.32 – 4.11 (m, 2H), 2.78 (d, *J* = 8.0 Hz, 1H), 2.63 (d, *J* = 14.1 Hz, 1H), 2.48 (d, *J* = 9.3 Hz, 2H), 2.35 (d, *J* =

5.5 Hz, 1H), 2.15 – 1.93 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 147.9, 137.0, 134.5, 128.5, 127.5, 126.2, 123.6, 121.6 (q, $J_{C\text{-}F}$ = 375 Hz), 118.3, 61.6, 57.6, 38.0, 31.2, 26.2, 14.0. IR (film) 1728.6, 1602.5, 1422.8 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{18}H_{19}F_3O_5S$ 405.0984; found 405.0978.



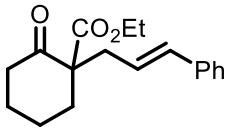
2-Cinnamylcyclopentan-1-one (2-S6). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with palladium allyl chloride dimer (0.146 g, 0.4 mmol, 0.02 equiv), dppf (0.665 g, 1.2 mmol, 0.06 mmol), and methanol (80 mL). The mixture was stirred at rt for 60 min, then cinnamyl alcohol (2.8 mL, 22 mmol, 1.1 equiv) was added to the orange mixture, and the resulting mixture was stirred at rt for 30 min. Cyclopentanone (2.1 mL, 20 mmol, 1 equiv) and pyrrolidine (0.33 mL, 4 mmol, 0.2 equiv) were added, and the mixture was then heated to 45 °C with stirring for 16 h. The reaction was quenched with cold saturated aqueous ammonium chloride (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 3.38 g (83%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 5H), 6.43 (d, J = 15.6 Hz, 1H), 6.24 – 6.08 (m, 1H), 2.65 (d, J = 10.0 Hz, 1H), 2.41 – 2.16 (m, 4H), 2.11 (d, J = 8.8 Hz, 1H), 2.01 (s, 1H), 1.81 (dddt, J = 14.7, 8.5, 4.3, 2.3 Hz, 1H), 1.63 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 220.4, 137.4,

131.8, 128.5, 127.6, 127.1, 126.0, 49.0, 38.2, 33.1, 29.0, 20.7. IR (film) 1732.7, 1597.2 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{14}H_{16}O$ 201.1280; found 201.1274.

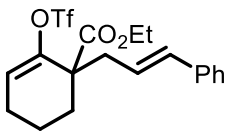


5-Cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (2-1m). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with THF (20 mL) and diisopropylamine (1.05 mL, 7.5 mmol, 1.5 equiv). The mixture was cooled to 0 °C, *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol, 1.5 equiv) was added dropwise, and the resulting solution was stirred at 0 °C for 30 min. The mixture was then cooled to -78 °C and a solution of 2-cinnamylcyclopentan-1-one (**2-S6**, 1.0 g, 5.0 mmol, 1 equiv) in THF (20 mL) was added dropwise over the course of 70 min. The reaction mixture was then stirred for 2 h at -78 °C, then a solution of *N*-(2-pyridyl)triflamide (2.61 g, 7.29 mmol, 1.2 equiv) in THF (10 mL) was added. The resulting mixture was warmed to -41 °C in CH_3CN/dry ice bath and stirred for 2 h. The reaction was quenched with water (20 mL) and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude material was purified via column chromatography on silica gel using 100:0 -> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 0.8675 g (52%) of the title compound as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 18.6 Hz, 4H), 7.26 (s, 1H), 6.49 (d, J = 15.8 Hz, 1H), 6.18 (d, J = 15.7 Hz, 1H), 5.71 (s, 1H), 3.04 (s, 1H), 2.57 (ddt, J = 11.1, 5.8, 2.9 Hz, 1H), 2.45 – 2.26 (m, 3H), 2.20 (s, 1H), 1.80 (d, J = 6.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3,

137.3, 132.6, 128.5, 127.2, 126.3, 126.1, 121.1 (q, $J_{C\text{-}F}$ = 315 Hz), 117.4, 43.0, 35.7, 26.7, 26.6. IR (film) 1656.6, 1495.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{15}F_3O_3S$ 333.0772; found 333.0767.

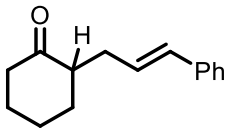


Ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (2-S7). The title compound was synthesized via a similar procedure described above for the preparation of ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (**2-S5**), except using ethyl-2-oxocyclohexanecarboxylate (3.2 mL, 20 mmol, 1 equiv), cinnamyl bromide (3.4 mL, 23.0 mmol, 1.15 equiv), and sodium hydride (0.712 g, 17.8 mmol, 0.89 equiv). The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 3.58 g (63%) of the title compound as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.12 (m, 5H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.24 – 6.09 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2. 73 (tdd, *J* = 11.5, 7.1, 1.4 Hz, 1H), 2.56 – 2.41 (m, 3H), 2.01 (ddt, *J* = 9.2, 6.2, 3.1 Hz, 1H), 1.81 – 1.57 (m, 4H), 1.57 – 1.49 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 171.5, 137.2, 133.2, 128.4, 127.2, 126.1, 125.1, 61.3, 41.2, 38.6, 36.1, 27.9, 27.5, 22.5, 14.2. IR (film) 1709.8 (2 overlapping peaks), 1597.9, 1495.7, cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{18}H_{22}O_3$ 287.1647; found 287.1642.



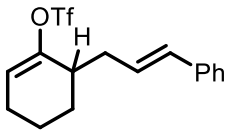
Ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (2-1h). The title compound was synthesized a similar procedure described above for the

preparation of ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**2-1l**), except using ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (**2-S7**) (1.13 g, 4.0 mmol, 1 equiv), LDA (6.73 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (2.409 g, 6.73 mmol, 1.7 equiv). The crude material was purified via column chromatography on silica gel using 100:0 -> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 1.06 g (64%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.12 (m, 5H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.12 (t, *J* = 15.4 Hz, 1H), 5.92 (s, 1H), 4.36 – 4.11 (m, 2H), 2.82 – 2.64 (m, 2H), 2.38 – 2.10 (m, 3H), 1.82 – 1.53 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 148.1, 137.0, 134.5, 128.5, 127.5, 126.2, 123.8, 120.3, 118.3 (q, $J_{C\text{-}F}$ = 318 Hz), 61.8, 50.5, 38.7, 32.3, 24.4, 18.6, 14.0. IR (film) 1730.3, 1677.1 cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{19}H_{21}F_3O_5S$ 419.1140; found 419.1135.

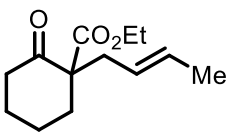


2-Cinnamylcyclohexan-1-one (2-S8). The title compound was synthesized via a similar procedure described above for the preparation of 2-cinnamylcyclopentan-1-one (**2-S5**), except using cyclohexanone (2.1 mL, 20 mmol, 1 equiv), cinnamyl alcohol (2.8 mL, 2.2 mmol, 1.1 equiv), palladium allyl chloride dimer (0.146 g, 0.4 mmol, 0.02 equiv), dppf (0.665 g, 1.2 mmol, 0.06 mmol), and pyrrolidine (0.33 mL, 4.0 mmol, 0.2 equiv). The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 2.74 g (63%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 4H), 7.19 (s, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.20 (t, *J* = 15.2 Hz, 1H), 2.73 – 2.60 (m, 1H), 2.43 (d, *J* = 15.8 Hz, 2H),

2.32 (d, *J* = 19.2 Hz, 1H), 2.25 – 2.00 (m, 3H), 1.88 (s, 1H), 1.67 (s, 2H), 1.41 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 137.5, 131.6, 128.5, 128.4, 128.3, 127.0, 126.0, 50.7, 42.1, 33.6, 27.9, 25.0. IR (film) 1705.24, 1597.9 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{18}O$ 215.1436; found 215.1430.

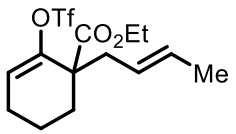


6-Cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (2-1i). The title compound was synthesized via a similar procedure to 5-cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (**2-1k**), except using 2-cinnamylcyclohexan-1-one (**2-S8**) (0.544 g, 2.54 mmol, 1 equiv), LDA (3.82 mmol, 1.5 equiv), and *N*-(2-pyridyl)triflamide (1.09 g, 3.05 mmol, 1.2 equiv). The crude material was purified via column chromatography on silica gel using 100:0 -> 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 0.660 g (75%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.13 (m, 5H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.23 – 6.04 (m, 1H), 5.83 (s, 1H), 2.62 (d, *J* = 10.1 Hz, 2H), 2.40 – 2.26 (m, 1H), 2.18 (s, 2H), 1.88 (s, 1H), 1.62 (dd, *J* = 49.8, 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 137.3, 132.7, 128.5, 127.2, 126.7, 126.1, 119.5, 118.5 (q, J_{C-F} = 319 Hz), 37.6, 35.1, 27.8, 24.3, 19.0. IR (film) 1680.2, 1494.3 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + NH_4^+]^+$ calcd for $C_{16}H_{17}F_3O_3S$ 364.1194; found 364.1189.



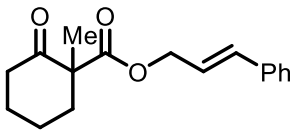
Ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (2-S9). The title compound was synthesized via a similar procedure described above for the preparation of ethyl 1-

cinnamyl-2-oxocyclopentane-1-carboxylate (**2-S4**), except using ethyl-2-oxocyclohexanecarboxylate (3.4 mL, 21.1 mmol, 1 equiv), crotyl bromide (2.5 mL, 24.3 mmol, 1.15 equiv), and sodium hydride (0.75 g, 18.8 mmol, 0.89 equiv). The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 2.26 g (48%) of the title compound as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 – 5.22 (m, 2H), 4.26 – 4.04 (m, 2H), 2.60 – 2.28 (m, 4H), 2.28 – 2.13 (m, 1H), 1.96 (ddd, *J* = 14.1, 5.2, 2.9 Hz, 1H), 1.81 – 1.51 (m, 6H), 1.42 (d, *J* = 16.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7, 171.6, 128.8, 125.6, 61.1, 41.1, 38.0, 35.7, 27.5, 22.5, 22.4, 17.9, 14.1. IR (film) 1710.4 (2 overlapping peaks), 1438.0 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{13}H_{20}O_3$ 225.1491; found 225.1485.

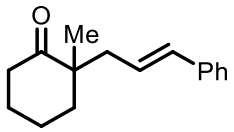


(*E*)-Ethyl-1-(but-2-en-1-yl)-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (2-1j). The title compound was synthesized via a similar procedure described above for the preparation of ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1l**), except using ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (**2-S9**) (0.98 g, 4.46 mmol, 1 equiv), LDA (7.6 mmol, 1.7 equiv), and *N*-(2-pyridyl)triflamide (2.66 g, 7.6 mmol, 1.7 equiv). The crude material was purified via column chromatography on silica gel using 100:0 -> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 0.623 g (40%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.57 – 5.45 (m, 1H), 5.28 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 16.3 Hz, 2H), 2.47 (s, 2H), 2.29 – 2.08 (m,

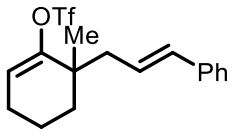
3H), 1.63 (d, *J* = 15.5 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 148.2, 130.2, 124.5, 120.0, 118.3 (q, $J_{C\text{-}F}$ = 318 Hz), 61.5, 50.3, 38.3, 32.0, 31.9, 24.4, 18.7, 13.9. IR (film) 1731.2, 1677.4, 1414.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{14}H_{19}F_3O_5S$ 357.0984; found 357.0978.



(±)-Cinnamyl 1-methyl-2-oxocyclohexane-1-carboxylate (2-S10). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with allyl 1-methyl-2-oxocyclohexane-1-carboxylate (1.169 g, 5.97 mmol, 1 equiv), Grubbs II catalyst (0.203 g, 0.239 mmol, 0.04 equiv), and copper iodide (68.1 mg, 0.358 mmol, 0.06 equiv). The flask was evacuated and backfilled with nitrogen, then and diethyl ether (30 mL, 0.2 M) and styrene (2.05 mL, 17.9 mmol, 3.0 equiv) were added to the mixture. The septum was replaced with a condenser and the mixture was heated to 40 °C with stirring for 15 h. The reaction mixture was cooled to rt, and concentrated *in vacuo* to yield a purple colored crude product. The crude product was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 0.904 g (63%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 6.71 – 6.58 (m, 1H), 6.31 – 6.18 (m, 1H), 4.87 – 4.72 (m, 2H), 2.57 – 2.41 (m, 2H), 2.09 – 1.95 (m, 1H), 1.83 (m, 1H), 1.78 – 1.58 (m, 2H), 1.54 – 1.42 (m, 1H), 1.32 (s, 3H), 1.04 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 172.9, 136.0, 134.8, 134.0, 128.6, 126.7, 122.4, 65.8, 57.2, 40.7, 38.2, 27.5, 22.6, 21.3. IR (film) 2935.8, 2867.1, 1709.7 (the two carbonyls are incidentally equivalent), 1495.5, 1449.5 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{17}H_{20}O_3Na$ 295.1305; found 295.1305.



2-Cinnamyl-2-methylcyclohexan-1-one (2-S11). A flame-dried Schlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with palladium acetate (27.8 mg, 0.124 mmol, 0.10 equiv), and triphenylphosphine (0.812 g, 3.10 mmol, 2.5 equiv). The flask was evacuated and backfilled with nitrogen, then tetrahydrofuran (25 mL, 0.1 M) and cinnamyl 1-methyl-2-oxocyclohexane-1-carboxylate (**2-S10**) (0.337 g, 1.24 mmol, 1.0 equiv) were added. The septum was replaced with a condenser and the reaction mixture was heated to 30 °C with stirring for 15 h. The mixture was then cooled to rt, diluted with diethyl ether, filtered through a pad of silica gel, and concentrated *in vacuo* to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 33.9 mg (12%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.18 – 6.06 (m, 1H), 2.47 (d, *J* = 15.0 Hz, 4H), 1.91 – 1.68 (m, 4H), 1.68 – 1.56 (m, 1H), 1.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.4, 137.4, 133.0, 128.4, 127.1, 126.0, 125.7, 48.9, 38.8, 38.6, 29.7, 27.4, 22.9, 21.1. IR (film) 3026.3, 2931.9, 2863.5, 1704.1, 1598.2, 1495.1 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{16}H_{21}O$ 229.1587; found 229.1586.



6-Cinnamyl-6-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (2-1k). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-

{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1l**), except using 2-cinnamyl-2-methylcyclohexan-1-one (**2-S11**) (1.13 g, 4.0 mmol, 1 equiv), LDA (6.73 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (2.409 g, 6.73 mmol, 1.7 equiv). The crude material was purified via column chromatography on silica gel using 100:0 –> 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 1.06 g (64%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.13 (m, 5H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.14 (ddd, *J* = 15.4, 8.1, 7.0 Hz, 1H), 5.76 (t, *J* = 4.1 Hz, 1H), 2.46 (ddd, *J* = 13.9, 7.0, 1.4 Hz, 1H), 2.31 (ddd, *J* = 13.9, 8.1, 1.2 Hz, 1H), 2.17 (ddd, *J* = 9.6, 5.7, 3.9 Hz, 2H), 1.82 (td, *J* = 9.6, 4.6 Hz, 1H), 1.73 – 1.58 (m, 2H), 1.59 – 1.48 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 137.3, 133.6, 128.5, 127.2, 126.1, 125.1, 118.4 (q, $J_{C\text{-}F}$ = 313 Hz), 117.3, 42.0, 38.7, 35.4, 24.7, 24.5, 18.2. IR (film) 3027.8, 2938.4, 1495.6, 1457.0, 1410.0 cm^{-1}. HRMS (Electron Ionization Impact TOF) m/z: $[M]^+$ calcd for $C_{17}H_{19}F_3O_3S$ 360.1007; found 360.1024.

Preparation and Characterization of Products

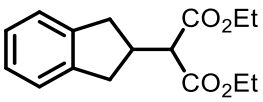
General Procedure for Pd-catalyzed Alkene Dialkylation Reactions on terminal alkenes, General Procedure A.

A flame-dried 4 mL vial equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 0.04 equiv), Brettphos (0.012 mmol, 0.06 equiv), and lithium *tert*-butoxide (0.28 mmol, 1.4 equiv). The aryl or alkenyl triflate (0.2 mmol, 1.0 equiv) was weighed in a separate 1 dram vial and diluted with toluene (1 mL, 0.2 M). This mixture was added to the reaction vessel and the appropriate nucleophile (0.24 mmol, 1.2 equiv) was added. Toluene (1 mL, 0.2M) was used to rinse the 1 dram vial and the solution was transferred to the reaction vessel. The vial was flushed with

nitrogen, capped, and heated to 95 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (1 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General procedure for Pd-catalyzed alkene dialkylation reactions on internal alkene substrates, General procedure B

A flame-dried 4 mL vial equipped with a stir bar and was cooled under a stream of nitrogen and charged with the appropriate triflate (0.2 mmol, 1.0 equiv), the appropriate palladium pre-catalyst (0.008 mmol, 0.04 equiv), the appropriate ligand (0.012 mmol, 0.06 equiv), lithium *tert*-butoxide (0.44 mmol, 2.2 equiv). The vial was purged with nitrogen and charged with toluene (0.8 M) and the appropriate malonate derivative (0.6 mmol, 3.6 equiv). The vial was capped and heated to the appropriate temperature with stirring until the starting material had been consumed. The mixture was cooled to rt, charged with phenanthrene (1 equiv; NMR internal standard), diluted with dichloromethane (1 mL), and quenched with saturated ammonium chloride (1 mL). The aqueous layer was extracted with dichloromethane (3 x 1 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

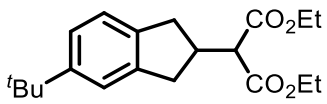


Diethyl 2-(2,3-dihydro-1*H*-inden-2-yl)malonate (2-6a). The title compound was prepared from 2-allylphenyl triflate (53.5 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column

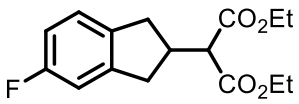
chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 51.7 mg (93%) of the title compound as a colorless solid (mp 33 – 35°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 2H), 7.16 – 7.13 (m, 2H), 4.22 (qd, *J* = 7.1, 2.7 Hz, 4H), 3.45 (d, *J* = 9.3 Hz, 1H), 3.25 – 3.03 (m, 3H), 2.83 – 2.69 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 142.1, 126.4, 124.4, 61.4, 56.8, 39.0, 37.3, 14.1; IR (film) 2980, 2840, 1744, 1727, 1476 cm^{-1}; HRMS (ESI^+ TOF) m/z: [M + H^+]$^+$ calcd for $C_{16}H_{20}O_4$ 277.1362; found 277.1434.

Diethyl 2-(2,3-dihydro-1*H*-inden-2-yl)malonate (2-6a). The title compound was prepared from 2-allylphenyl triflate (267 mg, 1.0 mmol) and diethyl malonate (183 µL, 1.2 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 232 mg (84%) of the title compound as a white solid (mp 33 – 35°C). Characterization data were identical to those listed above.

Diethyl 2-(2,3-dihydro-1*H*-inden-2-yl)malonate (2-6a). The title compound was prepared from 2-allylphenyl triflate (1.50 g, 5.63 mmol) and diethyl malonate (1.03 mL, 6.76 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 1.36 g (88%) of the title compound as a white solid (mp 33 – 35°C). Characterization data were identical to those listed above.

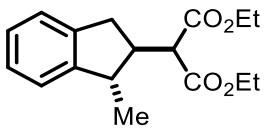


(±)-Diethyl 2-[5-(*tert*-butyl)-2,3-dihydro-1*H*-inden-2-yl]malonate (2-6b). The title compound was prepared from 2-allyl-4-*tert*-butylphenyl triflate (64.5 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 48.3 mg (77%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.20 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 4.28 – 4.16 (m, 4H), 3.46 (d, *J* = 8.9 Hz, 1H), 3.23 – 3.08 (m, 3H), 2.86 – 2.66 (m, 2H), 1.32 (s, 9H), 1.31 – 1.27 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 149.7, 142.1, 139.3, 124.0, 123.7, 121.4, 61.4, 57.1, 39.4, 37.6, 37.0, 34.7, 31.68, 14.3; IR (film) 1748, 1729, 1467 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{20}H_{28}O_4$ 333.199; found 333.206.

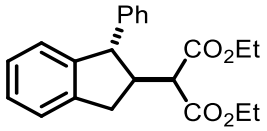


(±)-Diethyl 2-(5-fluoro-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6c). The title compound was prepared from 2-allyl-4-fluorophenyl triflate (56.8 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 46.5 mg (79%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.3, 5.2 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.82 (td, *J* = 8.9, 2.4 Hz, 1H), 4.25 – 4.16 (m, 4H), 3.44 (d, *J* = 9.1 Hz, 1H), 3.24 – 3.04 (m, 3H), 2.86 – 2.65 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 163.2, 161.2, 144.2 (d, *J* = 8.2 Hz), 137.4 (d, *J* = 2.5 Hz), 125.1 (d, *J* = 8.8 Hz), 113.2 (d, *J* = 22.6 Hz), 111.4 (d, *J* = 21.9 Hz), 61.6, 56.8, 39.7, 37.5, 37.5, 36.6, 14.2; IR (film) 2982, 1745, 1727, 1614,

1599, 1483 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{16}H_{19}FO_4$ 295.1267; found 295.134.

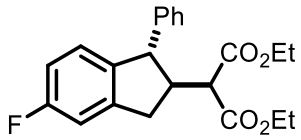


(±)-(1*S*,2*R*)-Diethyl 2-(1-methyl-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6d). The title compound was prepared from 2-(but-3-en-2-yl)phenyl triflate (56.0 mg, 0.2 mmol), and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A, except with (Brettphos)Pd(allyl)(Cl) (8.6 mg, 0.04 equiv) in place of $Pd(OAc)_2$. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 43.1 mg (75%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (401 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 4H), 4.24 – 4.15 (m, 4H) 3.51 (d, *J* = 8.2 Hz, 1H), 3.24 (dd, *J* = 16.1, 8.1 Hz, 1H), 3.08 (p, *J* = 6.8 Hz, 1H), 2.81 (dd, *J* = 16.1, 7.3 Hz, 1H), 2.69 (p, *J* = 8.0 Hz, 1H), 1.32 – 1.22 (m, 9H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.1, 168.8, 147.0, 141.4, 126.7, 126.66, 124.5, 123.6, 61.51, 61.45, 55.6, 46.9, 43.4, 35.8, 19.8, 14.3, 14.2; IR (film) 1741, 1728, 1464 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{22}O_4$ 291.1518; found 291.1591.



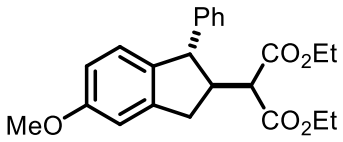
(1*S*,2*S*)-Diethyl 2-(1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6e). The title compound was prepared from 2-cinnamylphenyl trifluoromethanesulfonate (75.2 mg, 0.22 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol, 0.04 equiv), Brettphos (6.4 mg, 0.012 mmol, 0.06 equiv), with a reaction temperature of

65 °C for five hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 39.8 mg (51%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.22 – 6.97 (m, 7H), 6.93 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 4.27 (d, J = 9.0 Hz, 1H), 3.92 – 3.79 (m, 2H), 3.73 – 3.52 (m, 3H), 3.45 (dd, J = 15.7, 7.9 Hz, 1H), 3.32 – 3.22 (m, 1H), 2.96 (dd, J = 15.8, 8.9 Hz, 1H), 0.83 (t, J = 7.1 Hz, 3H), 0.73 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) δ 168.1, 167.9, 145.9, 143.4, 142.0, 127.8, 127.7, 127.6, 127.5, 126.6, 124.9, 124.2, 60.7, 60.6, 55.0 (2 peaks), 48.9, 36.0, 13.7, 13.4. IR (film) 1730.5, 1601.2 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H^{+}]$^{+}$ calcd for $C_{22}H_{24}O_4$ 353.1753; found 353.1747.



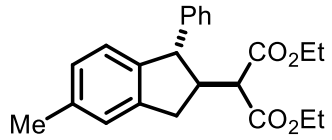
(±)-(1*S*,2*S*)-Diethyl 2-(5-fluoro-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6f). The title compound was prepared from 2-cinnamyl 4-fluorophenyl trifluoromethanesulfonate (64.7 mg, 0.18 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), palladium acetate (1.8 mg, 0.008 mmol, 0.04 equiv), Brettphos (6.4 mg, 0.012 mmol, 0.06 equiv), with a reaction temperature of 65 °C for five hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 31.0 mg (47%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR

(500 MHz, C_6D_6) δ 7.16 – 6.94 (m, 5H), 6.69 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.60 (t, *J* = 8.7 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.13 (d, *J* = 8.4 Hz, 1H), 3.95 – 3.76 (m, 2H), 3.65 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.61 – 3.46 (m, 2H), 3.29 – 3.17 (m, 2H), 2.80 (dd, *J* = 15.1, 8.0 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.73 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.0 (d, *J* = 34 Hz), 163.5 161.5, 144.1 (d, *J* = 9 Hz), 143.1, 141.3 (d, *J* = 1 Hz), 128.8, 127.9, 126.7, 126.0, 113.5 (d, *J* = 25 Hz), 111.1 (d, *J* = 23 Hz), 60.8 (d, *J* = 14 Hz), 54.5, 54.1, 49.2, 35.8 (2 peaks), 13.7, 13.4. IR (film) 1728.0, 1600.2, 1483.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{23}FO_4$ 371.1659; found 371.1653.

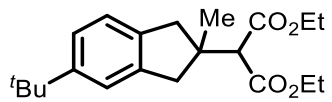


(±)-(1*S*,2*S*)-Diethyl 2-(5-methoxy-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6g). The title compound was prepared from 2-cinnamyl 4-methoxyphenyl trifluoromethanesulfonate (81.6 mg, 0.23 mmol), diethyl malonate (0.1 mL, 0.6 mmol), palladium acetate (1.8 mg, 0.008 mmol, 0.04 equiv), Brettphos (6.4 mg, 0.012 mmol, 0.06 equiv), with a reaction temperature of 65 °C for five hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 29.2 mg (35%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, C_6D_6) δ 7.19 (d, *J* = 7.2 Hz, 2H), 7.10 (s, 3H), 7.01 (s, 1H), 6.69 (d, *J* = 19.9 Hz, 2H), 6.61 (d, *J* = 10.3 Hz, 1H), 4.26 (d, *J* = 8.5 Hz, 1H), 3.97 – 3.78 (m, 2H), 3.76 – 3.53 (m, 3H), 3.49 – 3.36 (m, 1H), 3.30 (s, 3H), 3.04 – 2.87 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.2, 167.2, 159.5, 143.9,

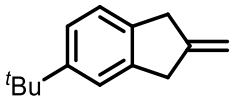
143.4, 137.8, 128.8, 128.3, 127.9, 127.8, 126.5, 125.6, 113.0, 109.5, 60.7, 54.8, 54.6, 54.3, 49.4, 36.1, 13.7. IR (film) 1727.7, 1608.5, 1588.8, cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{23}H_{26}O_5$ 383.1859; found 383.1853.



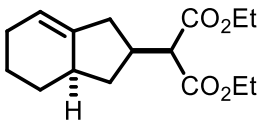
(±)- (1*S*,2*S*)-Diethyl 2-(5-methyl-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (2-6h). The title compound was prepared from 2-cinnamyl 4-methylphenyl trifluoromethanesulfonate (**5h**) (81.6 mg, 0.23 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 29.2 mg (35%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, C_6D_6) δ 7.23 – 7.14 (m, 1H), 7.09 (dd, *J* = 15.1, 7.6 Hz, 3H), 7.04 – 6.97 (m, 1H), 6.87 (s, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 4.28 (d, *J* = 8.7 Hz, 1H), 3.96 – 3.78 (m, 2H), 3.73 – 3.53 (m, 3H), 3.44 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.37 – 3.25 (m, 1H), 2.97 (dd, *J* = 15.7, 8.7 Hz, 1H), 2.11 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.2, 167.9, 143.7, 142.9, 142.1, 136.2, 128.9, 128.3, 127.5, 126.5, 124.9, 124.7, 60.7, 60.6, 54.8, 54.7, 49.2, 35.9, 20.9, 13.7, 13.6. IR (film) 2980.6, 1728.9, 1602.0, 1493.5, 1453.4 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{23}H_{26}O_4$ 367.1909; found 367.1904.



Diethyl 2-[5-(*tert*-butyl)-2-methyl-2,3-dihydro-1*H*-inden-2-yl]malonate (2-6i). The title compound was prepared from 4-*tert*-butyl-2-(2-methylallyl)phenyl triflate (67.3 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. This procedure afforded 9.7 mg (14%) of the title compound as a colorless oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 2H), 7.12 – 7.06 (m, 2H), 4.25 – 4.12 (m, 4H), 3.56 (s, 1H), 3.24 – 3.12 (m, 2H), 2.86 – 2.74 (m, 2H), 1.30 (s, 9H), 1.29 – 1.24 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.53, 149.43, 141.54, 138.71, 124.11, 123.37, 121.54, 61.01, 60.38, 45.55, 44.97, 44.44, 34.49, 31.55, 24.41, 14.08; IR (film) 2955, 1721, 1727, 1033 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{21}H_{30}O_4$ 347.2217; found 347.2220.

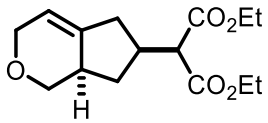


5-(tert-butyl)-2-methylene-2,3-dihydro-1H-indene (2-6i-a). The title compound was prepared from 4-*tert*-butyl-2-(2-methylallyl)phenyl triflate (67.3 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. This procedure afforded 23 mg (61%) of the title compound as a colorless oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.219 – 7.26 (m, 1H), 7.26 – 7.21 (m, 1H), 7.19 – 7.14 (m, 1H), 5.13 – 5.06 (m, 2H), 3.75 – 3.69 (m, 2H), 3.69 – 3.64 (m, 2H), 1.34 (s, 9H).



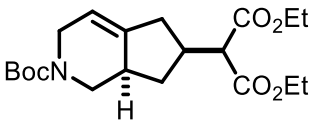
(±)-(2*S*,3a*R*)-Diethyl 2-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7a). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material

was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 45.4 mg (84%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.19 (qd, *J* = 7.1, 3.1 Hz, 4H), 3.17 (d, *J* = 9.9 Hz, 1H), 2.70 – 2.52 (m, 2H), 2.22 (br s, 1H), 2.11 – 2.01 (m, 1H), 2.03 – 1.91 (m, 4H), 1.77 (ddd, *J* = 12.3, 6.0, 3.2 Hz, 1H), 1.43 (m, 1H), 1.26 (td, *J* = 7.1, 1.9 Hz, 6H), 0.99 (m, 1H), 0.88 (q, *J* = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 169.0, 142.8, 118.1, 61.4, 57.8, 41.0, 38.6, 37.1, 35.3, 28.9, 25.3, 22.5, 14.3; IR (film) 1730, 1029 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{16}H_{24}O_4$ 281.1675; found 281.1747.

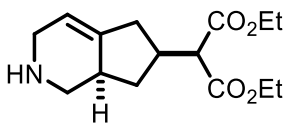


(±)-(6*S*,7a*R*)-Diethyl 2-(1,3,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-6-yl)malonate (2-7b). The title compound was prepared from 3-allyl-3,6-dihydro-2H-pyran-4-yl triflate (54.4 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 53.6 mg (95%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.25 – 4.09 (m, 6H), 4.09 – 3.99 (m, 1H), 3.19 (d, *J* = 9.2 Hz, 1H), 3.03 (t, *J* = 10.2 Hz, 1H), 2.75 – 2.63 (m, 2H), 2.56 (br s, 1H), 2.11 – 1.96 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.87 (q, *J* = 11.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 140.8, 116.8, 69.3, 65.1, 61.5, 57.4, 39.8, 37.1, 34.7, 34.0, 14.3; IR (film) 1750,

1727, 1461 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{22}O_5$ 305.1359; found 305.1362.

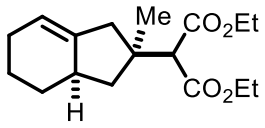


(±)-(6*S*,7a*R*)-Diethyl 2-[2-(*tert*-butoxycarbonyl)-2,3,5,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-yl]malonate (2-7c). The title compound was prepared from tert-butyl 3-allyl-4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2*H*)-carboxylate (67.1 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 25:75 hexanes:dichloromethane as the eluent. This procedure afforded 52.3 mg (76%) of the title compound as a colorless oil. Characterization data are for a mixture of rotamers; broadening is due to slow interconversion on the NMR time scale. ^1H NMR (500 MHz, C_6D_6) δ 5.09 (s, 1H), 4.57 – 4.15 (m, 2H), 4.11 – 3.82 (br m, 4H), 3.43 – 3.37 (m, 1H), 3.18 – 3.15 (m, 1H), 2.81 – 2.53 (m, 2H), 2.25 (br s, 1H), 2.21 – 2.12 (m, 1H), 2.07 – 1.95 (br m, 1H), 1.94 – 1.81 (m, 1H), 1.55 – 1.38 (m, 9H), 1.04 – 0.90 (m, 6H), 0.86 – 0.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 79.7, 61.5, 57.3, 40.2, 37.5, 35.1, 34.8, 28.6, 28.4, 14.2; IR (film) 1751, 1729, 1693 cm^{-1}; HRMS (ESI^+ TOF) m/z: 404.2044 (404.2044 calcd for $C_{20}H_{31}NO_6$, $M+Na^+$). HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{20}H_{31}NO_6$ 404.2044; found 404.2044.



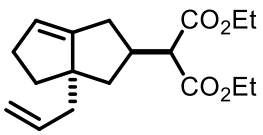
(±)-(6*S*,7a*R*)-diethyl 2-(2,3,5,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-yl)malonate (2-S12). In order to confirm the connectivity and stereochemistry of **2-7c**,

the boc group was cleaved by addition of trifluoroacetic acid (3 drops) to a solution of **2-7c** in dichloromethane; the resulting solution was stirred for 1 hour at rt. The solvent and excess trifluoroacetic acid were removed under reduced pressure and the product was washed with $NaHCO_3$, brine, and dried with $MgSO_4$. This procedure afforded 34.3 mg (89%) of the title compound as a colorless oil. This material was judged to be a >20:1 mixture of diastereomers by 1H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.37 - 3.29 (m, 2H), 3.18 (d, *J* = 9.5 Hz, 1H), 2.73 - 2.59 (m, 2H), 2.40 (br s, 1H), 2.33 – 2.23 (m, 1H), 2.11 – 1.97 (m, 2H), 1.49 – 1.37 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.88 (q, *J* = 11.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.8, 141.8, 116.8, 61.4, 57.5, 48.3, 44.5, 40.4, 36.9, 35.7, 35.0, 14.2; IR (film) 2983, 1782, 1730, 1148 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: [M + H$^+$]$^+$ calcd for $C_{15}H_{23}NO_4$ 282.1700; found 282.1706.

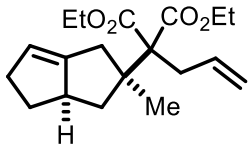


(±)-(2*S*,3a*R*)-Diethyl 2-(2-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7d). The title compound was prepared from 6-(2-methylallyl)cyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 55.6 mg (94%) of the title compound as a colorless oil. The compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.32 (s, 1H), 2.48 (d, *J* = 17.0 Hz, 1H), 2.39 (br s, 1H), 2.28 (d, *J* = 17.0 Hz, 1H), 2.02 - 1.90 (m, 3H), 1.87 – 1.73 (m,

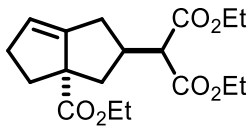
2H), 1.45 (tddd, *J* = 13.4, 10.3, 7.5, 2.9 Hz, 1H), 1.28 – 1.21 (m, 10H), 1.03 – 0.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 143.1, 118.1, 61.7, 61.3, 61.04, 61.03, 45.9, 44.1, 41.6, 38.7, 38.6, 29.0, 28.9, 25.3, 24.9, 22.6, 22.5, 14.3; IR (film) 1753, 1729 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{17}H_{26}O_4$ 317.1723; found 317.1729.



(±)-(2*S*,3a*S*)-Diethyl 2-(3a-allyl-1,2,3,3a,4,5-hexahydropentalen-2-yl)malonate (2-7e). The title compound was prepared from 5,5-diallylcyclopent-1-en-1-yl triflate (60 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 56.6 mg (92%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 16.9, 10.1, 7.9, 6.6 Hz, 1H), 5.22 (s, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 4.22 – 4.12 (m, 4H), 3.25 (d, *J* = 10.3 Hz, 1H), 3.09 (qt, *J* = 10.3, 6.4 Hz, 1H), 2.63 – 2.50 (m, 2H), 2.42 – 2.36 (m, 2H), 2.12 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.07 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.98 – 1.92 (m, 2H), 1.56 (dt, *J* = 12.4, 9.5 Hz, 1H), 1.25 (td, *J* = 7.1, 4.4 Hz, 6H), 1.03 (dd, *J* = 12.0, 10.5 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.9, 168.8, 153.9, 136.1, 119.1, 116.9, 61.41, 61.37, 59.3, 58.2, 41.5, 40.3, 39.9, 36.9, 36.1, 28.2, 14.3; IR (film) 1732, 1150 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{18}H_{26}O_4$ 307.1904; found 307.1909.

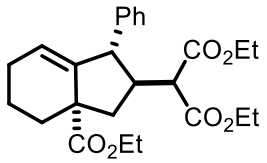


(±)-(2*S*,3a*R*)-Diethyl 2-allyl-2-(2-methyl-1,2,3,3a,4,5-hexahydropentalen-2-yl)malonate (2-7f). The title compound was prepared from (methylallyl)cyclopent-1-en-1-yl triflate (54.0 mg, 0.2 mmol), and diethyl allylmalonate (48 µL, 0.24 mmol) using General Procedure A, except with RuPhos (5.6 mg, 0.012 mmol) as ligand. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 40.8 mg (63%) of the title compound as a colorless oil. The compound was obtained as a 19:1 mixture of diastereomers as judged by ^{1}H NMR analysis. NOTE: The alkene was observed to isomerize in $CDCl_3$ to a 4:1 mixture of regioisomers. Data are for the major isomer. ^{1}H NMR (401 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.22 (s, 1H), 5.14 – 4.92 (m, 2H), 4.15 (m, 4H), 3.12 – 2.95 (br m, 1H), 2.82 – 2.38 (m, 5H), 2.10 (dtd, *J* = 12.0, 6.8, 1.2 Hz, 1H), 1.98 (ddd, *J* = 17.4, 4.5, 2.3 Hz, 1H), 1.83 – 1.60 (m, 2H), 1.50 – 1.33 (m, 1H), 1.24 (q, *J* = 7.3 Hz, 6H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.83, 170.79, 152.5, 135.2, 118.0, 117.5, 110.0, 65.5, 60.7, 51.9, 49.4, 43.2, 37.7, 37.3, 37.0, 32.4, 26.5, 14.1; IR (film) 1741, 1723, 1206 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + Na^{+}]^{+}$ calcd for $C_{19}H_{28}O_4$ 343.199; found 343.188.



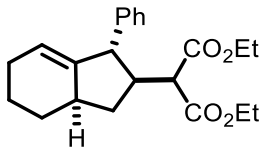
(±)-(1*R*,2*S*,3a*R)*-Diethyl 3a-(ethoxycarbonyl)-1,2,3,3a,4,5-hexahydropentalen-2-yl)malonate (2-7g). The title compound was prepared from ethyl 1-allyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (69.9 mg, 0.213 mmol) and

diethyl malonate (36 µL, 0.24 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol, 0.04 equiv), BrettPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for 14 h using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 48.2 mg (67%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.22–4.09 (m, 6H), 3.27 (d, *J* = 9.7 Hz, 1H), 3.17 (qd, *J* = 10.3, 5.0 Hz, 1H), 2.80 (dt, *J* = 14.9, 8.0 Hz, 1H), 2.66 – 2.53 (m, 1H), 2.46 (m, 4H), 2.04 (dd, *J* = 16.4, 6.0 Hz, 1H), 1.75 (dt, *J* = 12.8, 9.6 Hz, 1H), 1.27–1.23 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 168.5, 168.5, 149.6, 122.9, 65.5, 61.3, 60.7, 60.6, 57.6, 40.8, 40.6, 37.6, 36.9, 36.8, 28.8, 14.2, 14.1. IR (film) 2980.3, 2933.2, 2855.3, 1724.2, 1446.3 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{18}H_{26}O_6Na$ 361.1622; found 361.1617.



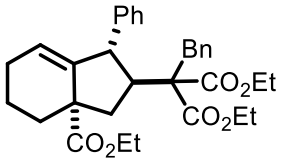
(±)-(1*S*,2*S*,3a*S*)-Diethyl 2-[3a-(ethoxycarbonyl)-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl] malonate (2-7h). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1i**) (83.0 mg, 0.20 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for fourteen hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 62.5 mg (73%) of the title compound as a colorless oil. The compound was obtained as a >20:1

mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.21 – 7.09 (m, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 5.33 (q, *J* = 3.2 Hz, 1H), 4.06 – 3.78 (m, 4H), 3.59 (dq, *J* = 10.5, 7.0 Hz, 1H), 3.49 (d, *J* = 6.9 Hz, 1H), 3.44 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.14 – 2.95 (m, 2H), 2.37 (dt, *J* = 12.6, 3.5 Hz, 1H), 1.94 – 1.82 (m, 1H), 1.73 (dtd, *J* = 18.3, 7.4, 3.8 Hz, 1H), 1.61 – 1.38 (m, 3H), 1.37 – 1.22 (m, 1H), 1.12 (td, *J* = 13.1, 3.8 Hz, 1H), 1.01 – 0.91 (m, 3H), 0.84 (dt, *J* = 17.9, 7.1 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 175.1, 167.9, 167.6, 144.5, 143.3, 129.4, 129.3, 127.5, 126.3, 123.8, 60.8, 60.6, 54.2, 53.5, 53.4, 44.6, 41.9, 33.0, 24.5, 19.2, 13.9, 13.7, 13.3. IR (film) 1724.1, 1605.6, 1446.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{25}H_{32}O_6$ 429.2277; found 429.2272.



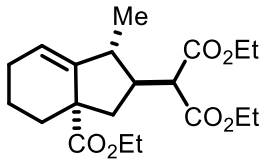
(±)-(1*R*,2*S*,3a*R*)-Diethyl 2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7i). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**2-1i**) (69.0 mg, 0.20 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for fourteen hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 54.1 mg (76%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 7.21 – 7.11 (m, 3H), 5.23 (p, *J* = 2.9 Hz, 1H), 4.15 (p, *J* = 7.0 Hz, 2H), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.63 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.40 (dt, *J* = 9.6, 2.6 Hz, 1H), 3.34 (d, *J* = 8.1

Hz, 1H), 2.78 – 2.66 (m, 1H), 2.58 – 2.45 (m, 1H), 2.31 (dt, *J* = 12.0, 6.1 Hz, 1H), 2.09 – 1.88 (m, 3H), 1.79 (dt, *J* = 12.7, 3.9 Hz, 1H), 1.51 – 1.38 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.16 – 0.95 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.3, 147.6, 145.2, 128.2, 128.1, 126.1, 120.3, 61.2, 61.0, 55.5, 53.1, 46.4, 41.3, 37.5, 28.8, 25.1, 22.2, 14.1, 13.7. IR (film) 1730.9, 1601.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{28}O_4$ 357.2066; found 357.2060.

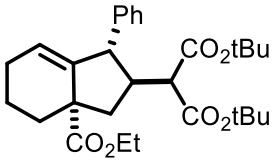


(±)-(1*S*,2*S*,3a*S*)-Diethyl 2-benzyl-2-[3a-(ethoxycarbonyl-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (2-7j). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1h**) (85.4 mg, 0.20 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), for 14 hours using General Procedure B, except with xylenes as solvent at 110 °C. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 53.3 mg (51%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 4H), 7.16 – 7.08 (m, 3H), 7.04 (dd, *J* = 7.1, 2.4 Hz, 2H), 5.43 (d, *J* = 2.5 Hz, 1H), 4.15 (dd, *J* = 29.8, 7.1 Hz, 2H), 4.03 – 3.84 (m, 2H), 3.70 (s, 2H), 3.10 (d, *J* = 13.9 Hz, 1H), 3.01 (d, *J* = 14.1 Hz, 1H),), 2.83 (dd, *J* = 12.6, 6.2 Hz, 1H), 2.27 (dt, *J* = 12.7, 3.5 Hz, 1H), 2.18 – 1.90 (m, 2H), 1.73 – 1.46 (m, 2H), 1.25 (dt, *J* = 14.2, 8.3 Hz, 5H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$)

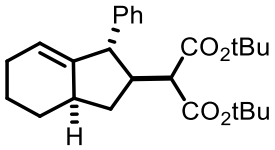
δ 175.9, 170.0, 169.9, 144.9, 144.5, 137.0, 130.2, 128.6, 128.0, 127.8, 126.6, 123.4, 62.2, 60.9, 60.8, 52.4, 51.8, 48.2, 40.9, 40.4, 33.6, 31.6, 24.5, 22.6, 18.9, 14.1, 13.9, 13.7. IR (film) 1720.8, 1601.5, 1495.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{32}H_{38}O_6$ 519.2747; found 519.2741.



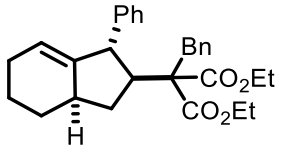
(±)-(1*R*,2*S*,3a*S*)-Diethyl 2-[3a-(ethoxycarbonyl)-1-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (2-7k). The title compound was prepared from ethyl (*E*)-1-(but-2-en-1-yl)-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1j**) (73.5 mg, 0.21 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for fourteen hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 40.1 mg (52%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (q, *J* = 3.1 Hz, 1H), 4.17 (ddt, *J* = 11.1, 7.6, 4.4 Hz, 6H), 3.39 – 3.30 (m, 1H), 3.26 (d, *J* = 6.0 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.23 (dt, *J* = 12.5, 3.4 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.98 (ddq, *J* = 14.6, 7.1, 3.5 Hz, 2H), 1.76 – 1.59 (m, 2H), 1.53 (ddd, *J* = 13.9, 6.9, 3.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 9H), 1.12 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 169.0, 168.4, 141.8, 114.8, 114.4, 61.3, 61.1 (2 peaks), 60.6, 54.8, 51.0, 49.7, 37.9, 31.7, 24.2, 19.6, 16.3, 14.1, 14.0. IR (film) 1725.2 (2 peaks), 1446.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{20}H_{30}O_6$ 367.2121; found 367.2115.



(±)-(1*S*,2*S*,3a*S*)-Di-*tert*-butyl 2-[3a-(ethoxycarbonyl)-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (2-7l). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**2-1h**) (83.6 mg, 0.20 mmol) and di-*tert*-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 64.1 mg (66%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.22 – 7.13 (m, 1H), 5.44 (q, *J* = 3.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.53 (dt, *J* = 11.0, 2.9 Hz, 1H), 3.20 (d, *J* = 5.8 Hz, 1H), 2.67 (dd, *J* = 12.2, 5.5 Hz, 1H), 2.63 – 2.49 (m, 1H), 2.34 (dt, *J* = 12.4, 3.3 Hz, 1H), 2.11 (ddd, *J* = 14.1, 7.2, 3.4 Hz, 1H), 2.03 (dq, *J* = 11.2, 3.8 Hz, 1H), 1.77 – 1.56 (m, 3H), 1.47 (m, 11H), 1.39 – 1.22 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 167.8, 167.7, 144.4, 143.2, 128.9, 128.2, 126.3, 123.8, 81.5, 81.3, 60.8, 55.1, 53.4, 52.9, 44.2, 40.8, 33.3, 28.0, 27.7, 24.5, 19.1, 14.3. IR (film) 2977.9, 2934.0, 1722.4 (2 peaks), 1496.0, 1453.7 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{29}H_{40}O_6$ 485.2903; found 485.2898.

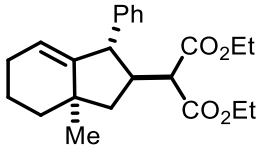


(±)-(1*R*,2*S*,3a*R*)-Di-*tert*-butyl 2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7m). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**2-1i**) (73.1 mg, 0.21 mmol) and di-*tert*-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 53.9 mg (62%) of the title compound as a white solid, mp: 79-81 °C. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.10 (m, 5H), 5.26 (m, 1H), 3.43 (dt, *J* = 9.2, 2.4 Hz, 1H), 3.19 (d, *J* = 7.0 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.56 – 2.43 (m, 1H), 2.31 (dt, *J* = 12.2, 6.3 Hz, 1H), 2.09 – 1.92 (m, 3H), 1.78 (dt, *J* = 13.0, 3.7 Hz, 1H), 1.47 (d, *J* = 1.2 Hz, 9H), 1.26 (s, 9H), 1.22 – 1.10 (m, 2H), 1.07 (dt, *J* = 12.6, 2.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 167.96, 147.7, 145.5, 128.3, 128.0, 126.0, 120.0, 81.4, 81.2, 56.8, 53.1, 46.1, 41.1, 36.8, 29.0, 28.0, 27.7, 25.1, 22.3. IR (film) 2977.9, 2929.2, 1720.2 (2), 1601.8, 1477.5, 1452.7 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H^{+}]$^{+}$ calcd for $C_{26}H_{36}O_4$ 413.2692; found 413.2686.



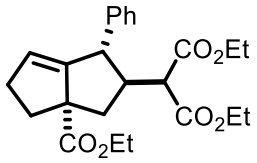
(±)-(1*R*,2*S*,3a*R*)-Diethyl 2-benzyl-2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7n). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**2-1i**) (57.6 mg, 0.17 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure B, except that the reaction was run in xylenes at 110 °C. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 39.0 mg (51%) of the

title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.06 (m, 9H), 6.95 (dd, *J* = 6.6, 3.0 Hz, 1H), 5.27 (q, *J* = 2.7 Hz, 1H), 4.05 – 3.87 (m, 3H), 3.88 – 3.76 (m, 1H), 3.70 – 3.61 (m, 1H), 3.20 – 3.14 (m, 2H), 3.09 (d, *J* = 14.0 Hz, 1H), 2.94 (dt, *J* = 10.6, 7.2 Hz, 1H), 2.40 (dt, *J* = 12.2, 7.2 Hz, 1H), 2.04 (ddt, *J* = 12.4, 5.3, 3.4 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.74 (ddd, *J* = 12.2, 6.1, 2.9 Hz, 1H), 1.52 – 1.34 (m, 2H), 1.32 – 1.18 (m, 1H), 1.19 – 1.04 (m, 4H), 1.02 (q, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 148.1, 147.5, 136.9, 130.2, 128.3, 127.8, 126.5, 119.2, 62.8, 60.8, 54.7, 51.9, 50.3, 40.5, 39.9, 36.0, 34.6, 29.2, 25.08, 22.1, 13.9. IR (film) 3027.9, 2979.3, 2929.1, 2854.1, 1725.4, 1602.4, 1495.3 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{29}H_{35}O_4$ 447.2530; found 447.2530.



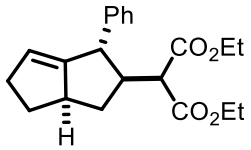
(±)-(1*R*,2*S*,3a*R*)-Diethyl 2-(3a-methyl-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (2-7o) The title compound was prepared from 6-cinnamyl-6-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (**2-1k**) (44.6 mg, 0.12 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 28.4 mg (62%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.11 (m, 5H), 5.19 (td, *J* = 3.6, 2.1 Hz, 1H), 4.24 – 4.07 (m, 2H), 3.77 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.58 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.47 (dq, *J* = 9.0, 2.8 Hz, 1H), 3.35 (d, *J* = 8.1 Hz,

1H), 2.98 (dddd, *J* = 11.9, 10.1, 8.1, 5.8 Hz, 1H), 2.11 – 1.90 (m, 3H), 1.82 – 1.60 (m, 3H), 1.38 – 1.15 (m, 8H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.3, 150.4, 144.3, 128.3, 128.2, 126.1, 120.6, 61.1, 61.0, 55.7, 53.5, 45.7, 43.6, 40.2, 36.8, 25.5, 24.5, 18.1, 14.1, 13.7. IR (film) 2977.3, 2933.5, 1731.4, 1492.9, 1452.0 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{23}H_{31}O_4$ 371.2217; found 371.2217.

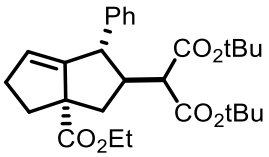


(±)-(1*S*,2*S*,3a*S*)-Diethyl 2-[3a-(Ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl] malonate (2-7p). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**2-1l**) (70.9 mg, 0.18 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for fourteen hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 53.8 mg (72%) of the title compound as a yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.08 (m, 4H), 5.58 (dt, *J* = 3.5, 1.7 Hz, 1H), 4.27 – 4.01 (m, 4H), 4.01 – 3.90 (m, 1H), 3.90 – 3.77 (m, 1H), 3.66 – 3.57 (m, 1H), 3.48 (d, *J* = 7.3 Hz, 1H), 3.24 (ddt, *J* = 8.8, 7.1, 1.8 Hz, 1H), 3.01 – 2.87 (m, 1H), 2.77 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.52 (ddd, *J* = 15.8, 8.7, 3.4 Hz, 1H), 2.33 (dd, *J* = 12.6, 6.5 Hz, 1H), 1.93 – 1.78 (m, 1H), 1.45 (t, *J* = 11.7 Hz, 1H), 1.23 (ddt, *J* = 25.1, 10.9, 7.2 Hz, 7H), 1.15 – 1.01 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 168.2, 166.6, 153.3, 142.8, 128.3, 127.7, 126.3, 125.9, 64.9, 61.5, 61.4, 60.7, 55.1, 54.3, 50.2, 47.1, 41.7, 39.5, 37.1, 29.7,

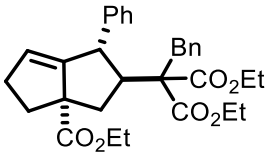
14.1. IR (film) 1725.0 (2 peaks), 1597.5 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{24}H_{30}O_6$ 415.2121; found 415.2115.



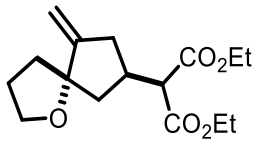
(±)-(1*R*,2*S*,3a*R)*-Diethyl 2-(1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl)malonate (2-7q). The title compound was prepared from 5-cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (**2-1m**) (62.4 mg, 0.19 mmol) and diethyl malonate (0.1 mL, 0.6 mmol), $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 0.04 equiv), SPhos (4.9 mg, 0.012 mmol, 0.06 equiv), at 95 °C for fourteen hours using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 18.8 mg (30%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 3H), 7.22 – 7.10 (m, 3H), 5.25 (tt, *J* = 3.2, 1.7 Hz, 1H), 4.23 – 4.05 (m, 2H), 3.98 – 3.84 (m, 1H), 3.84 – 3.71 (m, 1H), 3.47 (dd, *J* = 21.1, 8.3 Hz, 2H), 3.20 (d, *J* = 6.6 Hz, 1H), 3.10 – 2.97 (m, 1H), 2.59 (ddd, *J* = 7.0, 3.4, 1.7 Hz, 1H), 2.49 (dd, *J* = 9.7, 6.2 Hz, 1H), 2.29 (dt, *J* = 12.3, 6.4 Hz, 1H), 2.15 (dt, *J* = 13.2, 6.9 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.4, 155.7, 144.6, 128.3, 127.6, 126.2, 120.2, 61.2, 61.1, 55.7, 52.3, 51.5, 47.2, 37.2, 36.7, 32.1, 14.1, 13.7. IR (film) 2932.7, 2849.4, 1730.9, 1600.8, 1495.7, 1452.3 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{21}H_{26}O_4$ 343.1909; found 343.1904.



(±)-(1*S*,2*S*,3a*S*)-Di-*tert*-butyl 2-[3a-(ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl]malonate (2-7r). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**2-1l**) (80.8 mg, 0.2 mmol) and di-*tert*-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 54.5 mg (58%) of the title compound as a pale yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 4H), 7.16 (p, *J* = 3.5, 2.8 Hz, 1H), 5.63 – 5.55 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.64 (d, *J* = 8.4 Hz, 1H), 3.33 (dd, *J* = 6.8, 1.5 Hz, 1H), 3.20 – 3.08 (m, 1H), 2.94 (t, *J* = 8.5 Hz, 1H), 2.79 (dd, *J* = 12.3, 6.5 Hz, 1H), 2.53 (ddd, *J* = 15.7, 9.0, 2.8 Hz, 1H), 2.35 (dd, *J* = 12.6, 6.5 Hz, 1H), 1.95 – 1.81 (m, 1H), 1.56 – 1.40 (m, 10H), 1.31 (d, *J* = 1.6 Hz, 9H), 1.17 (td, *J* = 7.1, 1.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 167.8, 167.7, 153.3, 143.0, 128.3, 127.7, 126.2, 125.7, 81.6, 81.5, 64.8, 60.6, 56.9, 49.9, 47.0, 39.4, 39.1, 37.1, 28.0, 27.7, 14.1. IR (film) 2977.8, 2933.2, 1721.1 (the carbonyl peaks are incidentally equivalent), 1596.3, 1497.0, 1454.5 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{28}H_{38}O_6$ 471.2747; found 471.2741.

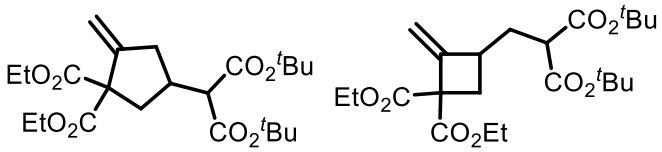


(±)-(1*S*,2*S*,3a*S*)-Diethyl 2-benzyl-2-[3a-(ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydro pentalen-2-yl]malonate (2-7s). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**2-1l**) (89.2 mg, 0.22 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure B, except that the reaction was run in xylenes at 110 °C. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 45.4 mg (41%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.02 (m, 10H), 5.54 (dt, *J* = 3.2, 1.5 Hz, 1H), 4.14 – 3.96 (m, 3H), 3.98 – 3.82 (m, 3H), 3.73 – 3.61 (m, 1H), 3.52 (dt, *J* = 10.3, 7.2 Hz, 1H), 3.19 (s, 2H), 3.02 – 2.81 (m, 2H), 2.52 (ddd, *J* = 15.6, 8.8, 3.3 Hz, 1H), 2.30 (dd, *J* = 12.7, 6.8 Hz, 1H), 1.84 (dt, *J* = 12.7, 9.4 Hz, 1H), 1.62 – 1.49 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 170.3, 170.2, 153.8, 143.7, 136.6, 130.2, 128.2, 127.9, 127.5, 126.7, 125.9, 124.4, 64.0, 63.0, 61.0, 60.8, 60.6, 52.4, 46.0, 40.6, 39.6, 37.9, 37.2, 14.0 (2 peaks), 13.5. IR (film) 2980.3, 1719.6, 1602.1, 1495.9, 1454.1 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{31}H_{36}O_6$ 505.2590; found 505.2585.



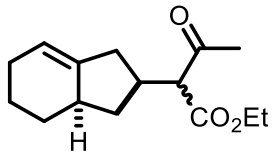
(±)-(5*S*,7*R*)-Diethyl 2-(9-methylene-1-oxaspiro[4.4]nonan-7-yl)malonate (2-9). The title compound was prepared from 1-(2-allyltetrahydrofuran-2-yl)vinyl triflate (57.3 mg, 0.2 mmol) and diethyl malonate (37 µL, 0.24 mmol) using General Procedure A. The crude

material was purified via column chromatography on silica gel using 95:5 -> 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 49.0 mg (82%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, C_6D_6) δ 4.96 (s, 1H), 4.88 (s, 1H), 4.07 – 3.84 (m, 4H), 3.75 – 3.59 (m, 2H), 3.31 – 3.18 (m, 1H), 3.23 – 3.09 (m, 1H), 2.89 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.29 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.16 (ddt, *J* = 16.3, 9.5, 2.6 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.71 – 1.52 (m, 3H), 1.46 (dd, *J* = 12.9, 10.7 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.12, 168.09, 154.1, 106.3, 88.0, 66.3, 60.63, 60.62, 57.0, 43.8, 36.8, 35.7, 34.4, 26.0, 13.7; IR (film) 1749, 1728, 1445, 1025 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{16}H_{24}O_5$ 297.1624; found 297.1697.



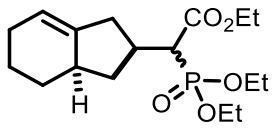
(±)-Diethyl 4-(1,3-di-tert-butoxy-1,3-dioxopropan-2-yl)-2-methylenecyclopentane-1,1-dicarboxylate (11) and (±)-Diethyl 3-(3-(tert-butoxy)-2-(tert-butoxycarbonyl)-3-oxopropyl)-2-methylenecyclobutane-1,1-dicarboxylate (2-11a and 2-11b). The title compounds were prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (37.3 mg, 0.1 mmol) and di-*tert*-butyl malonate (26.7 µL, 0.12 mmol) using General Procedure A except XPhos (6 mol %) was used as ligand, 1,4-dioxane was used as solvent, and the reaction was conducted for 1 hr. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 33.4 mg (76%) combined yield of [**2-11a**] and [**2-11b**] in a 1:2.5 regioisomeric mixture which was determined by ^{1}H

NMR analysis. Characterization data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 – 5.3 (ddd, *J* = 12.4, 2.9, 1.3 Hz, 1.4H), 5.25 (t, *J* = 2.0 Hz, 0.43H), 5.14 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.30 – 4.15 (m, *J* = 14.2, 7.2, 5.9, 3.2 Hz, 5.7H), 3.16 (t, *J* = 7.6 Hz, 1H), 3.09 – 2.95 (m, 1.4H), 2.75 – 2.55 (m, 2.3H), 2.31 – 2.18 (m, 1.4H), 2.15 (ddd, *J* = 13.9, 7.8, 6.1 Hz, 1H), 2.09 – 2.00 (m, 0.8H), 1.94 (ddd, *J* = 13.9, 9.4, 7.4 Hz, 1H), 1.50 – 1.41 (m, 26H), 1.25 (td, *J* = 7.2, 6.1 Hz, 9.7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 169.1, 168.7, 168.6, 147.8, 146.5, 112.8, 110.6, 81.75, 81.73, 81.72, 61.84, 61.78, 61.76, 61.7, 59.3, 58.6, 51.8, 40.0, 38.5, 36.9, 32.9, 32.1, 29.8, 28.1, 19.0, 14.19, 14.14, 14.12.

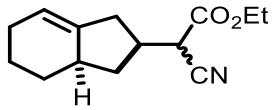


(±)-Ethyl (2*S*,3a*R*)-2-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)-3-oxobutanoate (2-12a). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and ethyl acetoacetate (31 µL, 0.24 mmol) using the General Procedure A. The crude material was purified via column chromatography on silica gel using 99:1 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 40.5 mg (81%) of the title compound. The compound was obtained as a 1:1 mixture of diastereomers, epimeric at the stereocenter between the carbonyl groups as indicated by the structure above, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (401 MHz, $CDCl_3$) δ 5.35 (s, 0.5H), 5.32 (s, 0.5H), 4.28 – 4.10 (m, 2H), 3.25 (dd, *J* = 10.1, 8.2 Hz, 1H), 2.75 – 2.50 (m, 2H), 2.22 (d, *J* = 3.1 Hz, 4H), 2.10 – 1.71 (m, 6H), 1.51 – 1.34 (m, 1H), 1.29 – 1.25 (m, 3H), 1.05 – 0.89 (m, 1H), 0.88 – 0.71 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 202.9, 169.33, 169.28, 142.7, 142.5, 118.3, 118.2, 66.4, 66.2, 61.4, 41.1, 40.8, 38.6, 38.59, 36.9, 35.2, 35.2, 29.3, 29.0, 28.9, 25.30, 25.29, 22.5, 22.4, 14.3; IR (film) 1735,

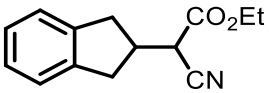
1710 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{15}H_{22}O_3$ 273.1569; found 273.1461.



(±)-(2*S*,3a*R*)-Ethyl 2-(diethoxyphosphoryl)-2-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)acetate (2-12b). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (500 mg, 1.85 mmol), and triethyl phosphonoacetate (440 µL, 2.22 mmol) using General Procedure A except with lithium hexamethyldisilazide (774 mg, 4.625 mmol) as base. The crude material was purified via column chromatography on silica gel using 50:50 -> 15:85 hexanes:ethyl acetate as the eluent. This procedure afforded 332 mg (52%) of the title compound as a yellow oil. The compound was obtained as a 1:1 mixture of diastereomers, epimeric at the stereocenter adjacent to the ester group as indicated by the structure above, as judged by ^1H NMR analysis. Data are for the mixture ^1H NMR (401 MHz, $CDCl_3$) δ 5.39 (s, 0.5H), 5.35 (s, 0.5H), 4.35 – 3.98 (m, 6H), 2.84 – 2.54 (m, 2.5H), 2.35 – 2.09 (m, 2H), 2.07 – 1.86 (m, 4H), 1.85 – 1.71 (m, 1H), 1.50 – 1.37 (m, 1H), 1.41 – 1.14 (m, 9H), 1.14 – 0.73 (m, 2.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.21, 169.06, 142.83, 142.20, 117.97, 62.46, 61.21, 52.14, 51.09, 41.32, 40.64, 39.63, 39.51, 39.42, 36.28, 36.24, 36.15, 36.11, 35.92, 35.79, 35.43, 28.65, 28.58, 25.19, 25.14, 22.32, 22.30, 16.40, 16.36, 14.17; IR (film) 1731 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{29}O_5P$ 345.1753; found 345.1825.

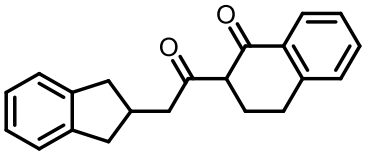


(±)-(2*S*, 3a*R*)-Ethyl 2'-cyano-2-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl acetate (2-12c). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol), ethyl cyanoacetate (26 µL, 0.24 mmol), using General Procedure A, except with Pd(allyl)BrettphosCl (8.6 mg, 0.012 mmol), as catalyst, BrettPhos was added (6.4 mg, 0.012 mmol), cesium carbonate (91.2 mg, 0.28 mmol) as base, and 1,4 dioxane (2 mL, 0.1M) as solvent. The crude material was purified via column chromatography on silica gel using 65:35 -> 50:50 hexanes:dichloromethane as the eluent. This procedure afforded 22.8 mg (50%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of diastereomers, epimeric at the CN-bearing stereocenter, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (401 MHz, $CDCl_3$) δ 5.43 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.48 (dd, *J* = 11.3, 6.5 Hz, 1H), 2.69 – 2.50 (m, 2H), 2.35 – 1.91 (m, 6H), 1.85 – 1.71 (m, 1H), 1.51 – 1.34 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.16 – 0.97 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 141.3, 141.1, 119.32, 119.27, 115.9, 62.8, 42.70, 42.65, 41.1, 41.0, 38.5, 37.9, 37.7, 34.8, 34.0, 28.7, 25.2, 22.3, 14.2; IR (film) 2248, 1743, 1453 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{14}H_{19}NO_2$ 234.1416; found 234.1493.



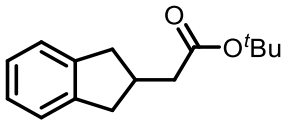
(±)-Ethyl 2-cyano-2-(2,3-dihydro-1H-inden-2-yl)acetate (2-13a). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol), ethyl cyanoacetate (26 µL, 0.24 mmol), using General Procedure A, except with Pd(allyl)BrettphosCl (8.6 mg, 0.012 mmol) as catalyst, additional BrettPhos (6.4 mg, 0.012 mmol), Cs_2CO_3 (91.2 mg, 0.28 mmol) as base, and dioxane (2 mL, 0.1M) as solvent. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This

procedure afforded 22.0 mg (47%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of diastereomers, epimeric at the CN-bearing stereocenter, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 4H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.64 (dd, *J* = 6.8, 1.7 Hz, 1H), 3.25 – 3.08 (m, 3H), 2.99 (dd, *J* = 15.5, 7.4 Hz, 1H), 2.92 (dd, *J* = 14.5, 6.7 Hz, 1H), 1.34 (t, *J* = 7.2, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.59, 140.95, 140.93, 126.91, 126.87, 124.54, 124.46, 115.72, 62.85, 42.08, 42.04, 39.96, 37.07, 36.56, 14.02; IR (film) 2908, 2242, 1737, 1460, 743 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + Na^{+}]^{+}$ calcd for $C_{14}H_{15}NO_2$ 247.1441; found 247.1445.

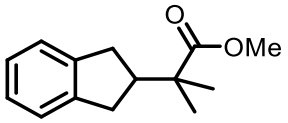


(±)-2-[2-(2,3-Dihydro-1*H*-inden-2-yl)acetyl]-3,4-dihydronaphthalen-1(2*H*)-one (2-13b). The title compound was prepared from 2-allylphenyl triflate (53.5 mg, 0.2 mmol) and 2-acetyl-1-tetralone (45.2 mg, 0.24 mmol) using General Procedure A, except with LiHMDS (87.0 mg, 0.52 mmol) as the base, and xylenes (2 mL) as the solvent, and a reaction temperature of 130 °C. The crude material was purified via column chromatography on silica gel using 65:35 hexanes:dichloromethane as the eluent. This procedure afforded 24.5 mg (40%) of the title compound as a yellow solid, mp 77–80 °C, that contained ca 5% of inseparable impurities. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 1H), 7.37 (td, *J* = 7.4, 1.5 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.20 – 7.14 (m, 3H), 7.14 – 7.08 (m, 2H), 3.15 (dd, *J* = 15.6, 7.7 Hz, 2H), 3.01 – 2.91 (m, 1H), 2.85 – 2.79 (m, 2H), 2.73 – 2.61 (m, 4H), 2.58 (dd, *J* = 8.3, 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.95, 177.67, 142.75, 140.82, 131.88, 131.30, 127.51, 126.85, 126.26, 125.90, 124.50, 106.06,

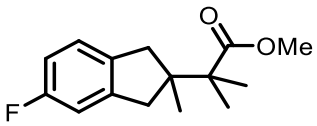
41.46, 39.10, 36.22, 28.28, 22.52; IR (film) 3062, 2926, 2833, 1712, 1666, 1586, 1554, 1294 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{21}H_{20}O_2$ 327.1356; found 327.1360.



***tert*-Butyl 2-(2,3-dihydro-1*H*-inden-2-yl)acetate (2-14a).** The title compound was prepared from 2-allylphenyl triflate (266.5 mg, 1 mmol) and *tert*-butyl acetate (165 µL, 1.4 mmol) using General Procedure A, except with LiHMDS (368 mg, 2.2 mmol) as the base. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent to afford a mixture of the desired product and a side product resulting from C-arylation of the ester. In order to separate these compounds, the material was further reacted with 0.5 g of AD-alpha-mix in a 1:1 solution of *tert*-butyl alcohol and water (1.6 mL: 1.6 mL) for 12 h at rt to oxidize the alkene in the undesired product. The oxidation reaction was then quenched with sodium sulfite and stirred at rt for 30 min. The aqueous layer was extracted with ethyl acetate (3 x 5 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane. This procedure afforded 24.5 mg (24%) of the title compound as a colorless oil.^{1}H NMR (401 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 7.16 – 7.10 (m, 2H), 3.12 (dd, *J* = 15.5, 7.8 Hz, 2H), 2.85 (p, *J* = 7.6 Hz, 1H), 2.64 (dd, *J* = 15.5, 7.4 Hz, 2H), 2.41 (d, *J* = 7.5 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.27, 142.80, 126.20, 124.44, 80.22, 41.41, 38.92, 36.34, 28.13; IR (film) 2248, 1743, 1453 cm^{-1}; IR (film) 2969, 2921, 1724, 1480 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{15}H_{20}O_2$ 255.1356; found 255.1360.

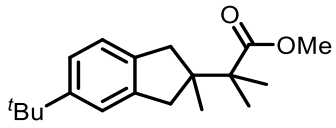


Methyl 2-(2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (2-14b). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 37.1 mg (85%) of the title compound as a colorless oil.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 7.14 – 7.10 (m, 2H), 3.68 (s, 3H), 2.96 – 2.86 (m, 2H), 2.85 – 2.74 (m, 3H), 1.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.11, 142.89, 126.33, 124.45, 77.41, 77.16, 76.91, 51.85, 47.83, 44.52, 34.56, 23.09; IR (film) 1726 cm^{-1}; HRMS (ESI^+ TOF) m/z: [M + H^+]$^+$ calcd for $C_{14}H_{18}O_2$ 219.3180; found 219.1380.

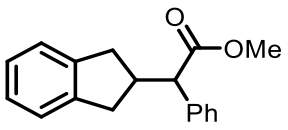


(±)-Methyl 2-(5-fluoro-2-methyl-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (2-14c). The title compound was prepared from 4-fluoro-2-(2-methylallyl)phenyl triflate (56.8 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base and RuPhos (5.6 mg, 0.012 mmol) as the ligand. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 11.5 mg (23%) of the title compound as a colorless oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.2, 5.3 Hz, 1H), 6.90 – 6.75 (m, 2H), 3.65 (s, 3H), 3.23 (dd, *J* = 25.1, 16.1 Hz, 2H), 2.48 (dd, *J* = 16.0, 11.5 Hz, 2H), 1.25 (s, 6H), 1.03 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ

177.52, 162.65, 161.27, 144.36 (d, *J* = 8.0 Hz), 137.55, 125.58 (d, *J* = 8.7 Hz), 112.94 (d, *J* = 22.2 Hz), 111.71 (d, *J* = 21.8 Hz), 51.51, 48.95, 47.81, 47.56, 42.50, 42.49, 41.50, 29.69, 23.75, 22.09, 22.07, 19.01; IR (film) 2929, 1723, 1141 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{15}H_{19}FO_2$ 273.1369; found 273.1267.

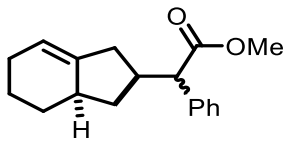


(±)-Methyl 2-[5-(*t*ert-butyl)-2-methyl-2,3-dihydro-1*H*-inden-2-yl]-2-methylpropanoate (2-14d). The title compound was prepared from 4-*tert*-butyl-2-(2-methylallyl)phenyl triflate (67.3 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A except with LiHMDS (73.6 mg, 0.44 mmol) as the base and RuPhos (5.6 mg, 0.012 mmol) as the ligand. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. This procedure afforded 13.7 mg (24%) of the title compound as a colorless oil. ^1H NMR (401 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 1H), 3.65 (s, 3H), 3.31 – 3.20 (m, 2H), 2.54 – 2.43 (m, 2H), 1.31 (s, 9H), 1.26 (s, 6H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.71, 149.22, 142.08, 139.24, 124.23, 123.15, 121.69, 51.44, 48.47, 47.61, 42.47, 41.89, 34.49, 31.59, 23.94, 22.14; IR (film) 2952, 1728, 1144 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{19}H_{28}O_2$ 306.2428; found 306.2436.



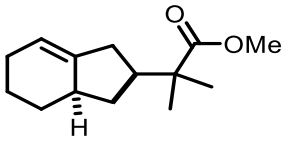
(±)-Methyl 2-(2,3-dihydro-1*H*-inden-2-yl)-2-phenylacetate (2-14e). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and methyl 2-phenylacetate (35 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44

mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane -> 65:35 hexanes:dichloromethane as the eluent. This procedure afforded 45.8 mg (86%) of the title compound as a white solid, mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 4H), 7.24 – 7.19 (m, 1H), 7.18 – 7.06 (m, 3H), 3.70 (s, 3H), 3.56 (d, *J* = 10.5 Hz, 1H), 3.34 – 3.15 (m, 2H), 2.84 – 2.66 (m, 2H), 2.50 (dd, *J* = 15.7, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.03, 142.53, 142.33, 138.30, 128.70, 128.28, 127.45, 126.32, 126.29, 124.48, 124.34, 56.98, 51.96, 42.92, 38.19, 37.06; IR (film) 2941, 1725, 1577, 1451, 1433 cm^{-1}; HRMS (ESI^{+} TOF) m/z: [M + Na^{+}]$^{+}$ calcd for $C_{18}H_{18}O_2$ 289.1199; found 289.1203.

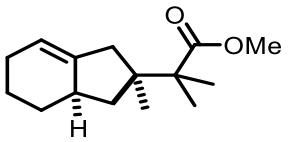


(±)-(2*S*,3a*R*)-Methyl 2-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)-2-phenylacetate (2-14f). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and methyl 2-phenylacetate (35 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane -> 65:35 hexanes:dichloromethane as the eluent. This procedure afforded 29.2 mg (54%) of the title compound as a colorless oil. The compound was obtained as a 2:1 mixture of diastereomers epimeric at the stereocenter alpha to the carbonyl group, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.30 – 7.24 (m, 1H), 5.40 (m, 0.67H), 5.30 (s, 0.34H), 3.66 (s, 3H), 3.29 (d, *J* = 10.6 Hz, 1H), 2.84 – 2.61 (m, 1.67H), 2.28 (br s, 0.33H), 2.24 – 2.09 (m, 1.35H), 2.05 – 1.94 (m, 3H), 1.92 – 1.83 (m, 0.67H), 1.83 – 1.70 (m, 1.34H), 1.66 – 1.55 (m, 1H), 1.51 – 1.34 (m,

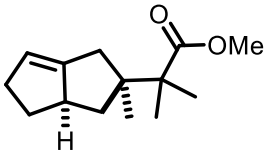
1H), 1.09 – 0.86 (m, 1.34H), 0.67 (q, *J* = 11.6 Hz, 0.67H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.15, 143.38, 143.06, 138.54, 128.51, 128.19, 128.14, 127.25, 127.22, 117.78, 117.75, 58.17, 57.91, 51.86, 51.83, 41.21, 40.88, 40.82, 40.74, 39.42, 38.66, 35.92, 35.01, 28.91, 28.83, 25.19, 25.17, 22.38, 22.35; IR (film) 2914, 2833, 1731, 1430 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{18}H_{22}O_2$ 271.1693; found 271.1695.



(±)-(2*S*,3a*R*)-Methyl 2-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)-2-methylpropanoate (2-14g). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane -> 65:35 hexanes:dichloromethane as the eluent. This procedure afforded 39.1 mg (88%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.65 (s, 3H), 2.38 – 2.12 (m, 3H), 2.09 – 1.90 (m, 4H), 1.87 – 1.70 (m, 2H), 1.50 – 1.36 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 1.06 – 0.95 (m, 1H), 0.94 – 0.83 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.47, 143.62, 117.60, 77.41, 77.16, 76.91, 51.72, 45.66, 44.10, 41.42, 35.44, 31.85, 28.98, 25.39, 22.74, 22.61, 22.57; IR (film) 1730, 1151 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{14}H_{22}O_2$ 223.1693; found 223.1682.

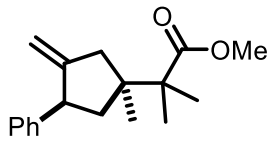


(±)-(2*S*,3a*R*)-Methyl 2-methyl-2-(2-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)propanoate (2-14h). The title compound was prepared from 6-(2-methylallyl)cyclohex-1-en-1-yl triflate (56.9 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base and RuPhos (5.6 mg, 0.012 mmol) as the ligand. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 24.7 mg (52%) of the title compound as a colorless oil. The compound was obtained as an 11:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (401 MHz, $CDCl_3$) δ 5.32 (s, 1H), 3.63 (s, 3H), 2.65 – 2.54 (m, 1H), 2.38 (br s, 1H), 2.05 – 1.88 (m, 4H), 1.82 – 1.72 (m, 1H), 1.52 (dd, *J* = 12.1, 7.0 Hz, 1H), 1.48 – 1.37 (m, 1H), 1.33 (t, *J* = 12.1 Hz, 1H), 1.14 (s, 6H), 1.01 (s, 3H), 1.00 – 0.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.90, 143.91, 117.22, 51.28, 47.96, 45.16, 42.34, 40.66, 38.95, 29.04, 25.17, 24.87, 22.47, 21.61, 21.58; IR (film) 1922, 1726, 1432, 1135 cm^{-1}; HRMS (ESI^{+} TOF) m/z: [M + Na^{+}]$^{+}$ calcd for $C_{19}H_{28}O_2$ 306.2428; found 306.2436.



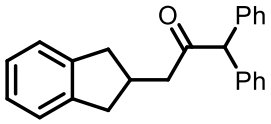
(±)-(2*S*,3a*R*)-Methyl 2-methyl-2-(2-methyl-1,2,3,3a,4,5-hexahydropentalen-2-yl)propanoate (2-14i). The title compound was prepared from 5-(2-methylallyl)cyclopent-1-en-1-yl triflate (54.0 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using

General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base and RuPhos (5.6 mg, 0.012 mmol) as the ligand. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 22.2 mg (50%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. NMR spectra were acquired in C_6D_6, as some (ca 5%) isomerization of the alkene occurred when spectra were acquired in $CDCl_3$. ^{1}H NMR (401 MHz, C_6D_6) δ 5.24 (s, 1H), 3.31 (s, 3H), 2.95 (br s, 1H), 2.80 – 2.67 (m, 1H), 2.66 – 2.53 (m, 1H), 2.51 – 2.38 (m, 1H), 2.11 – 2.05 (m, 1H), 1.84 – 1.74 (m, 1H), 1.52 – 1.29 (m, 4H), 1.14 (s, 6H), 1.03 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 176.54, 152.91, 117.81, 52.08, 50.53, 49.78, 48.01, 41.82, 37.24, 34.74, 32.35, 25.21, 21.47, 21.43; IR (film) 2943, 2839, 1726, 1132 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{14}H_{22}O_2$ 223.1693; found 223.1690.



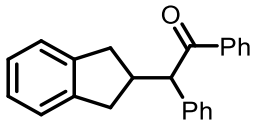
(±)-(1*S*,4*R*)-Methyl 2-methyl-2-(1-methyl-3-methylene-4-phenylcyclopentyl)propanoate (2-16). The title compound was prepared from 5-methyl-3-phenylhexa-1,5-dien-2-yl triflate (64.1 mg, 0.2 mmol) and methyl isobutyrate (28 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base and RuPhos (5.6 mg, 0.012 mmol) as the ligand. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 28 mg (52%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H

NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 5.00 (s, 1H), 4.59 (s, 1H), 3.79 – 3.70 (m, 1H), 3.67 (s, 3H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.21 (d, *J* = 16.3 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.92 – 1.84 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H) 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.64, 155.32, 145.32, 128.35, 128.14, 126.05, 108.75, 51.39, 48.86, 47.74, 45.59, 44.87, 43.20, 22.23, 21.63, 21.60; IR (film) 2968, 1726, 1142 cm^{-1}; HRMS (ESI^{+} TOF) m/z: [M + H^{+}]$^{+}$ calcd for $C_{18}H_{24}O_2$ 273.1849; found 273.1847.

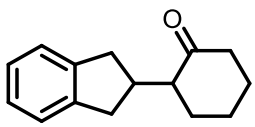


3-(2,3-Dihydro-1*H*-inden-2-yl)-1,1-diphenylpropan-2-one (2-17a). The title compound was prepared from 2-allylphenyl triflate (533 mg, 2.0 mmol) and 1,1-diphenylacetone (505 mg, 2.4 mmol) using General Procedure A, except with LiHMDS (736 mg, 4.4 mmol) as the base. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent to afford a mixture of the desired product and a side product resulting from C-arylation of the ester. In order to separate these compounds, the material was further reacted with 1.2 g of AD-alpha-mix in a 1:1 solution of tertbutyl alcohol and water (4 mL: 4 mL) for 12 h at rt to oxidize the alkene in the undesired product. The oxidation reaction was then quenched with sodium sulfite and stirred at rt for 30 min. The aqueous layer was extracted with ethyl acetate (3 x 8 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate. This procedure afforded 158 mg (24%) of the title compound as a colorless oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.26 – 7.19 (m, 6H), 7.14 – 7.05 (m, 4H), 5.10 (s, 1H), 3.08 (dd, *J* = 15.6,

7.8 Hz, 2H), 2.90 (dt, *J* = 14.9, 7.5 Hz, 1H), 2.74 (d, *J* = 7.1 Hz, 2H), 2.46 (dd, *J* = 15.5, 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.95, 142.79, 138.35, 129.01, 128.78, 127.30, 126.28, 124.48, 64.35, 48.73, 39.07, 35.10; IR (film) 3020, 2902, 2833, 1713, 1492, 903 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{24}H_{22}O$ 349.1563; found 349.1566.

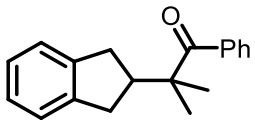


(±)-2-(2,3-Dihydro-1*H*-inden-2-yl)-1,2-diphenylethan-1-one (2-17b). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and deoxybenzoin (47.1 mg, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 50.1 mg (81%) of the title compound as a colorless oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 2H), 7.52 – 7.45 (m, 1H), 7.43 – 7.36 (m, 4H), 7.35 – 7.28 (m, 2H), 7.26 – 7.20 (m, 1H), 7.18 – 7.08 (m, 4H), 4.57 (d, *J* = 10.7 Hz, 1H), 3.53 – 3.37 (m, 1H), 3.27 (dd, *J* = 15.8, 7.7 Hz, 1H), 2.77 – 2.54 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.76, 142.91, 142.54, 138.59, 137.06, 132.94, 128.97, 128.65, 128.59, 128.55, 127.27, 126.27, 126.24, 124.54, 124.37, 58.86, 43.16, 38.65, 37.04; IR (film) 3026, 2938, 2836, 1675, 1596, 698 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{23}H_{20}O$ 313.1587; found 313.1592.



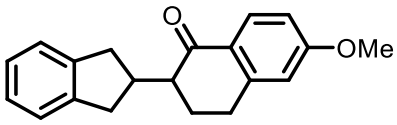
(±)-2-(2,3-Dihydro-1*H*-inden-2-yl)cyclohexan-1-one (2-17c). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and cyclohexanone (50 µL, 0.48

mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 65:35 hexanes:dichloromethane as the eluent. The product was further purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate. This procedure afforded 30.5 mg (71%) of the title compound as a white solid, mp: 67-69°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 2H), 7.15 – 7.10 (m, 2H), 3.24 (dd, *J* = 15.9, 7.9 Hz, 1H), 3.03 (dd, *J* = 15.3, 7.9 Hz, 1H), 2.76 (p, *J* = 8.5 Hz, 1H), 2.64 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.55 (dd, *J* = 15.9, 8.9 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.39 – 2.30 (m, 1H), 2.19 – 2.11 (m, 1H), 2.09 – 2.00 (m, 1H), 1.95 – 1.87 (m, 1H), 1.80 – 1.64 (m, 2H), 1.60 – 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.08, 143.51, 142.67, 126.14, 126.00, 124.29, 124.13, 56.25, 42.23, 39.38, 38.22, 36.64, 32.17, 28.24, 24.64; IR (film) 2931, 2857, 1704, 744 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{15}H_{18}O$ 215.1430; found 215.1432.

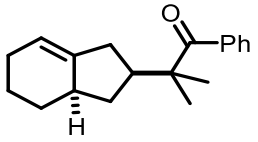


2-(2,3-Dihydro-1*H*-inden-2-yl)-2-methyl-1-phenylpropan-1-one (2-17d). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and phenyl isopropyl ketone (36 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 90:10 hexanes:dichloromethane -> 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 35.5 mg (67%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.38 (m, 2H), 7.21 – 7.16 (m, 2H), 7.15 – 7.11 (m, 2H), 3.24 – 3.13

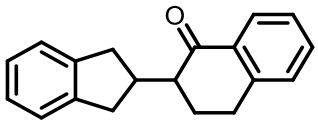
(m, 1H), 2.99 – 2.78 (m, 4H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.32, 142.62, 139.58, 130.65, 128.12, 127.43, 126.25, 124.33, 49.99, 46.61, 34.30, 22.93; IR (film) 2914, 1669, 1593, 956, 740 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{20}O$ 265.1587; found 265.1592.



(±)-2-(2,3-Dihydro-1*H*-inden-2-yl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (2-17e). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and 6-methoxy-1-tetralone (42.3 mg, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 65:35 hexanes:dichloromethane -> 50:50 hexanes:dichloromethane as the eluent. This procedure afforded 42.1 mg (72%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.15 – 7.11 (m, 2H), 6.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.71 – 6.67 (m, 1H), 3.85 (s, 3H), 3.18 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.15 – 2.91 (m, 4H), 2.87 (dd, *J* = 15.7, 8.4 Hz, 1H), 2.74 (dd, *J* = 15.0, 8.2 Hz, 1H), 2.62 (ddd, *J* = 9.8, 7.4, 4.1 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.02 – 1.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.64, 163.38, 146.16, 143.53, 142.78, 129.87, 126.34, 126.19, 126.09, 124.28, 124.16, 113.15, 112.39, 55.41, 51.94, 38.75, 37.81, 36.74, 28.45, 26.21; IR (film) 2963, 2832, 1660, 1601, 1251, 742 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{20}H_{20}O_2$ 293.1536; found 293.1541.

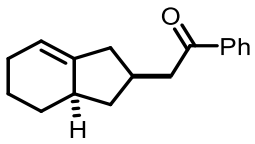


(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-2-methyl-1-phenylpropan-1-one (2-17f). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and phenyl isopropyl ketone (36 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 50:50 hexanes:dichloromethane as the eluent under high pressure. This procedure afforded 28.4 mg (53%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 2H), 7.46 – 7.42 (m, 1H), 7.41 – 7.35 (m, 2H), 5.35 (s, 1H), 2.63 – 2.53 (m, 1H), 2.33 – 2.25 (m, 1H), 2.21 – 2.13 (m, 1H), 2.08 – 1.90 (m, 4H), 1.86 – 1.73 (m, 2H), 1.42 (m, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.07 – 0.90 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.74, 143.29, 139.83, 130.43, 128.01, 127.34, 117.60, 49.61, 44.55, 41.15, 35.16, 31.72, 28.81, 25.22, 23.03, 22.38; IR (film) 2925, 2837, 1673, 958 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{24}O$ 269.1900; found 269.1905.

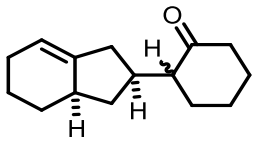


(±)-2-(2,3-Dihydro-1*H*-inden-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (2-17g). The title compound was prepared from 2-allylphenyl triflate (53.3 mg, 0.2 mmol) and 1-tetralone (32 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 37.8 mg (72%) of the title compound as a white solid, mp 61–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 –

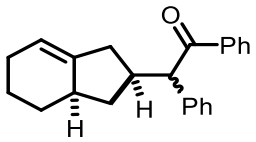
7.25 (m, 1H), 7.25 – 7.20 (m, 2H), 7.18 – 7.13 (m, 2H), 3.22 (dd, *J* = 15.7, 8.0 Hz, 1H), 3.18 – 2.97 (m, 4H), 2.89 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.78 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.69 (ddd, *J* = 10.1, 7.6, 4.2 Hz, 1H), 2.30 – 2.22 (m, 1H), 2.08 – 1.97 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.93, 143.76, 143.47, 142.74, 133.21, 132.72, 128.71, 127.46, 126.64, 126.26, 126.16, 124.32, 124.21, 52.32, 38.72, 37.83, 36.73, 28.12, 26.25; IR (film) 3009, 2877, 1671, 1597, 734 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{19}H_{18}O$ 285.1250; found 285.1255.



(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1-phenylethan-1-one (2-17h). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and acetophenone (28 μL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 99.5:0.5 hexanes:ethyl acetate as the eluent. This procedure afforded 25.0 mg (52%) of the title compound as a colorless oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ7.95 (d, *J* = 7.7 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 5.37 (s, 1H), 3.06 – 2.94 (m, 2H), 2.73 – 2.64 (m, 1H), 2.56 – 2.47 (m, 1H), 2.23 (br s, 1H), 2.16 – 2.09 (m, 1H), 2.06 – 1.94 (m, 3H), 1.93 – 1.86 (m, 1H), 1.82 – 1.74 (m, 1H), 1.49 – 1.40 (m, 1H), 1.05 – 0.96 (m, 1H), 0.84 (q, *J* = 11.4 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 200.22, 143.91, 137.35, 133.03, 128.69, 128.22, 117.73, 45.15, 41.34, 40.73, 37.19, 33.57, 29.15, 25.39, 22.62; IR (film) 1682, 1448 cm^{-1}; HRMS (ES) $[M]^+$ calcd for $C_{17}H_{20}O$ 240.1514; found 240.1517.

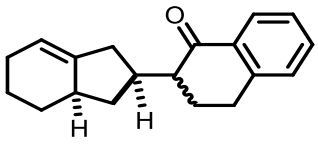


(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)cyclohexan-1-one (2-17i). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and cyclohexanone (50 µL, 0.48 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 29.5 mg (68%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of diastereomers epimeric at the stereocenter alpha to the carbonyl group, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 – 5.30 (m, 1H), 2.75 – 2.66 (m, 0.5H), 2.56 – 2.47 (m, 0.5H), 2.41 – 2.33 (m, 1H), 2.33 – 2.12 (m, 4H), 2.13 – 2.06 (m, 1H), 2.06 – 1.91 (m, 5H), 1.90 – 1.69 (m, 4H), 1.69 – 1.59 (m, 1H), 1.57 – 1.37 (m, 2H), 1.02 – 0.92 (m, 1H), 0.76 – 0.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.62, 213.49, 144.03, 143.49, 117.41, 117.06, 57.36, 56.70, 42.09, 41.90, 41.47, 40.87, 39.04, 38.06, 36.80, 36.63, 36.24, 34.37, 32.21, 32.13, 28.93, 28.80, 28.32, 28.28, 25.25, 25.20, 24.56, 24.11, 22.42; IR (film) 2920, 2853, 1709, 1447 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{15}H_{22}O$ 219.1743; found 219.1747.



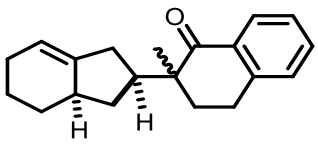
(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1,2-diphenylethan-1-one (2-17j). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg,

0.2 mmol) and deoxybenzoin (47.1 mg, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate as the eluent. The material was further purified via column chromatography on silica gel using 90:10 hexanes:dichloromethane -> 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 45.4 mg (72%) of the title compound as a viscous, colorless oil. The compound was obtained as a 1:1 mixture of diastereomers epimeric at the stereocenter alpha to the carbonyl group, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.53 – 7.47 (m, 1H), 7.45 – 7.33 (m, 4H), 7.33 – 7.26 (m, 2H), 7.25 – 7.19 (m, 1H), 5.34 (s, 1H), 4.39 – 4.29 (m, 1H), 2.98 – 2.84 (m, 1H), 2.84 – 2.73 (m, 0.5H), 2.30 (br s, 0.5H), 2.24 – 2.13 (m 1H), 2.05 – 1.73 (m, 5H), 1.66 – 1.55 (m, 1H), 1.50 – 1.38 (m, 1H), 1.04 – 0.92 (m, 1H), 0.89 – 0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.18, 199.77, 143.95, 143.37, 138.83, 138.80, 137.24, 137.05, 132.81, 132.78, 128.76, 128.73, 128.60, 128.51, 128.49, 128.46, 128.35, 127.01, 117.58, 117.48, 60.37, 59.63, 41.36, 41.08, 41.00, 40.58, 39.80, 38.93, 36.45, 34.99, 28.97, 25.22, 22.38; IR (film) 2914, 2847, 1678, 1596, 659 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{23}H_{24}O$ 317.1900; found 317.1906.



(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (2-17k). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and 1-tetralone (32 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified

via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 42.1 mg (79%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of diastereomers epimeric at the stereocenter alpha to the carbonyl group, as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 – 7.98 (m, 1H), 7.47 – 7.42 (m, 1H), 7.32 – 7.27 (m, 1H), 7.25 -7.20 (m, 1H), 5.37 (s, 1H), 3.11 – 3.02 (m, 1H), 3.00 – 2.88 (m, 1H), 2.68 – 2.54 (m, 1H), 2.50 – 2.35(m, 2H), 2.28 – 2.17 (m, 2H), 2.17 – 2.08 (m, 1H) 2.08 – 1.92 (m, 5H), 1.84 – 1.73 (m, 1H), 1.50 – 1.37 (m, 1H), 1.08 – 0.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.29, 143.83, 143.71, 143.69, 143.47, 133.03, 132.99, 132.71, 132.67, 128.64, 128.61, 127.43, 127.39, 126.51, 117.61, 117.32, 52.62, 52.09, 41.43, 41.08, 38.76, 38.01, 36.25, 36.10, 35.60, 34.27, 28.90, 28.80, 27.95, 27.41, 26.31, 26.01, 25.27, 25.23, 22.44; IR (film) 2934, 2869, 1675, 1598 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{19}H_{22}O$ 289.1563; found 223.1569.

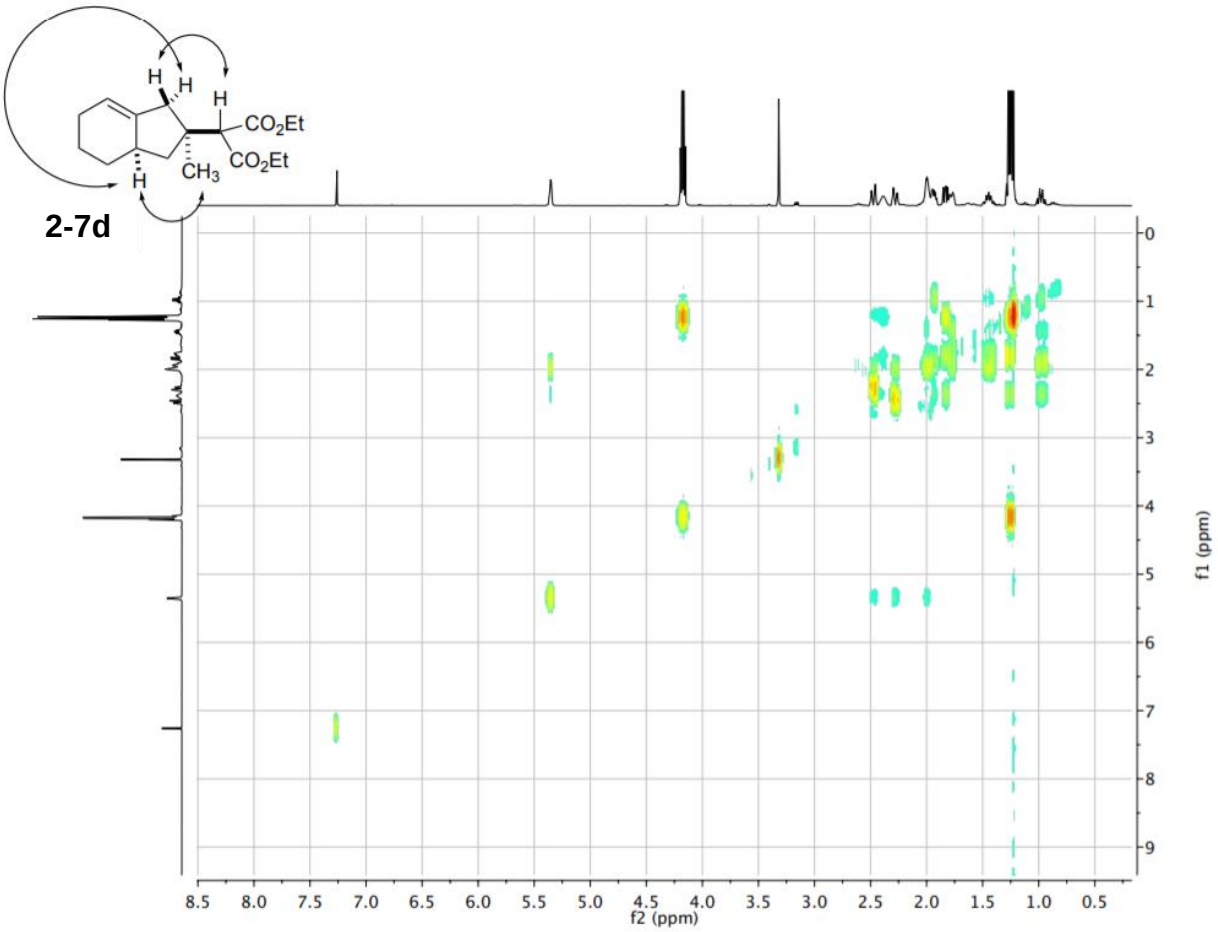


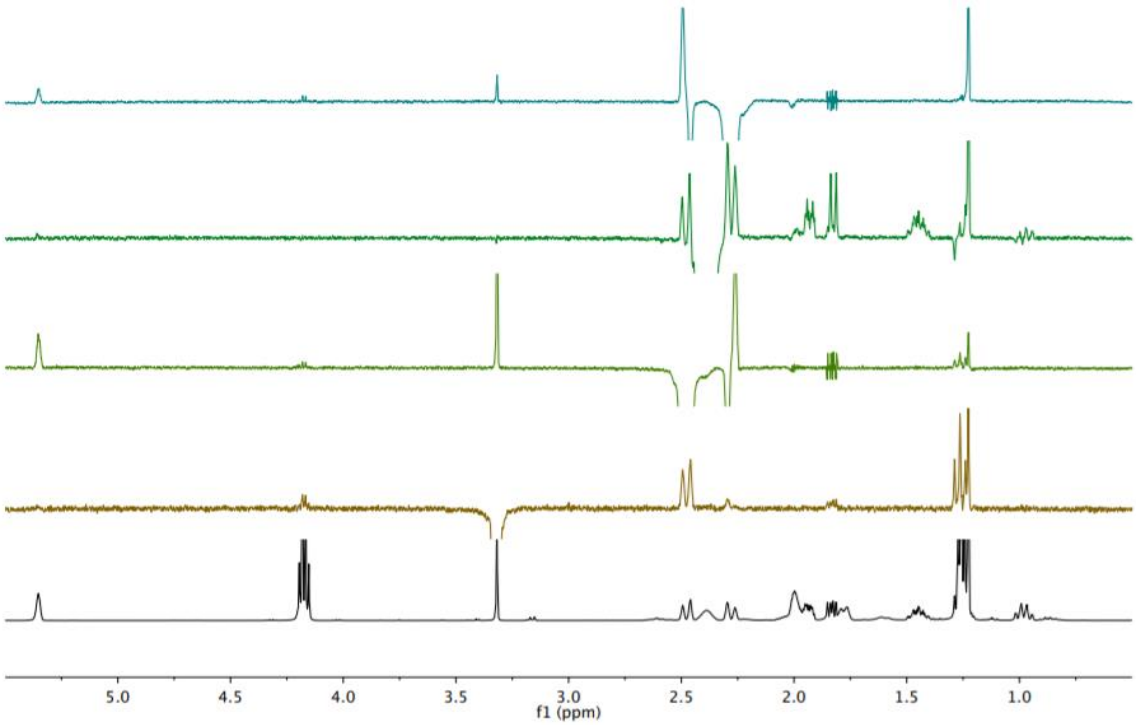
(±)-(2*S*,3a*R*)-2-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2-17l). The title compound was prepared from 6-allylcyclohex-1-en-1-yl triflate (54.1 mg, 0.2 mmol) and 2-methyl-1-tetralone (37 µL, 0.24 mmol) using General Procedure A, except with LiHMDS (73.6 mg, 0.44 mmol) as the base. The crude material was purified via column chromatography on silica gel using 80:20 hexanes:dichloromethane as the eluent. This procedure afforded 31.6 mg (56%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of diastereomers epimeric at the stereocenter alpha to the carbonyl group, as judged by ^{1}H

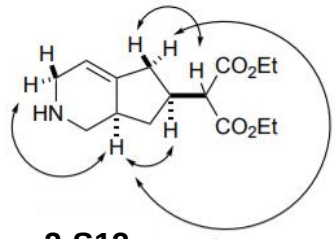
NMR analysis. Data are for the mixture. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 1H), 7.48 – 7.41 (m, 1H), 7.33 – 7.26 (m, 1H), 7.23 – 7.18 (m, 1H), 5.35 (s, 1H), 3.12 – 2.98 (m, 1H), 2.97 – 2.87 (m, 1H), 2.56 – 2.36 (m, 1.5H), 2.25 – 2.12 (m, 2H), 2.10 - 2.04 (m, 1H), 2.03 – 1.84 (m, 5H), 1.82 – 1.72 (m, 1H), 1.71 – 1.63 (m, 0.5H), 1.49 – 1.33 (m, 1H), 1.13 (s, 1.5H), 1.12 (s, 1.5H), 1.08 – 0.94 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.51, 202.36, 188.00, 143.51, 143.46, 143.22, 143.14, 132.86, 132.83, 132.03, 128.55, 128.00, 127.97, 126.57, 117.49, 117.43, 46.25, 46.02, 41.23, 41.15, 40.74, 40.62, 35.00, 34.65, 32.15, 32.09, 31.64, 30.97, 28.89, 28.82, 25.28, 25.26, 25.22, 22.43, 22.39, 18.75; IR (film) 2926, 2856, 1680, 1600, 1222, 747 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{20}H_{24}O$ 281.1900; found 281.1902.

2.13 Assignment of Relative Stereochemistry

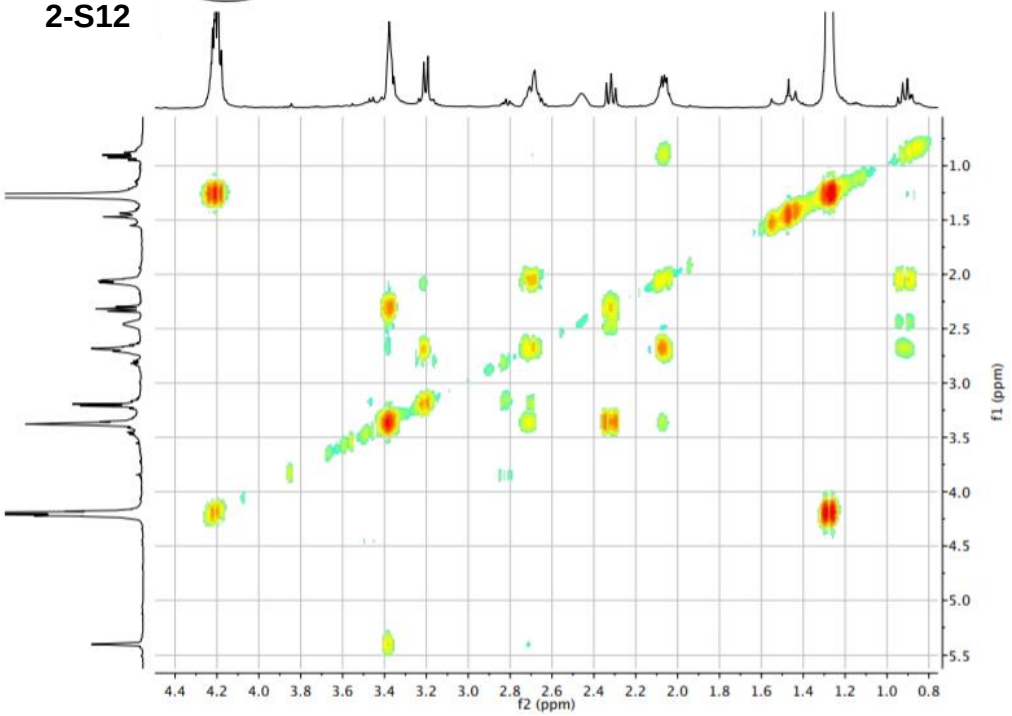
The relative stereochemistry of products **2-7d**, **2-7c** (via **2-S12**), **2-7e**, **2-7p**, **2-7k**, **2-7o**, **2-6e**, **2-16**, and **2-17h** was assigned on the basis of ^{1}H NMR nOe studies. The data for these studies is provided below, along with the key nOe signals. The relative stereochemistry of all other products was assigned based on analogy to **2-7d**, **2-7c** (via **2-S12**), **2-7e**, **2-7p**, **2-7k**, **2-7o**, **2-6e**, **2-16**, or **2-17h**.

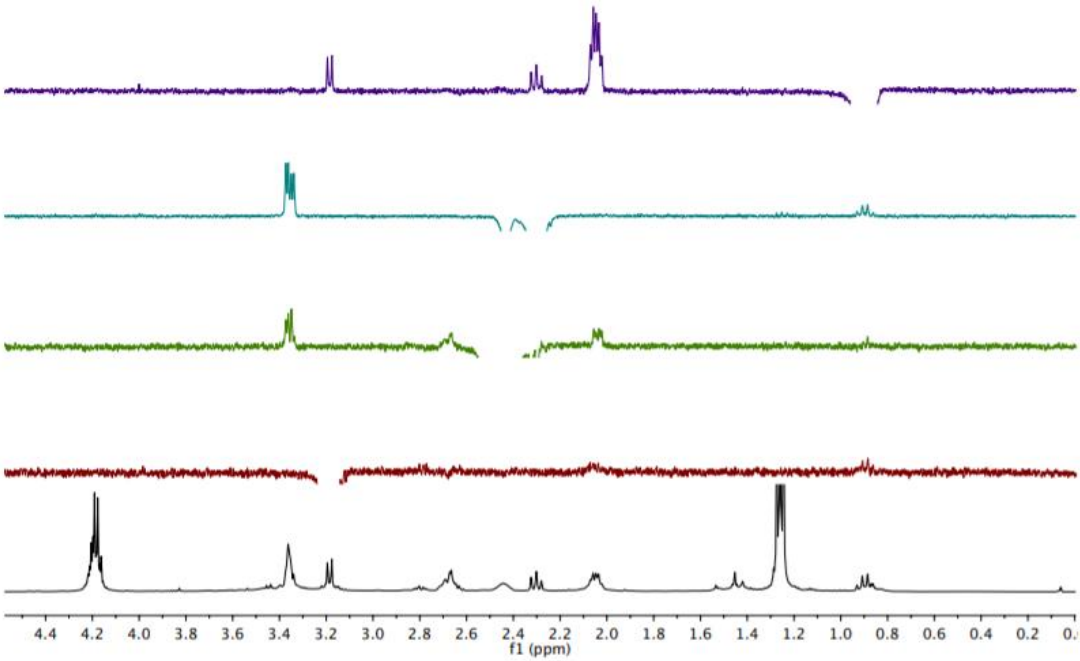

H
H
H
CO2Et
CO2Et
CH3
H
2-7d
f2 (ppm)
f1 (ppm)

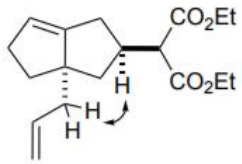

f1 (ppm)



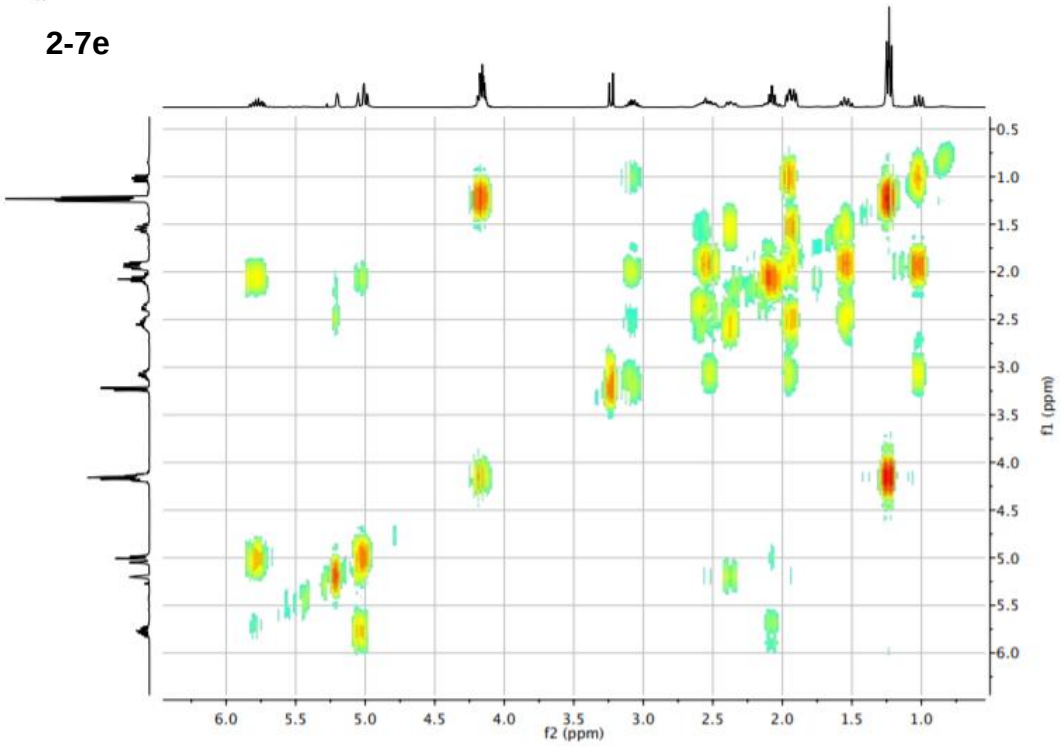
2-S12

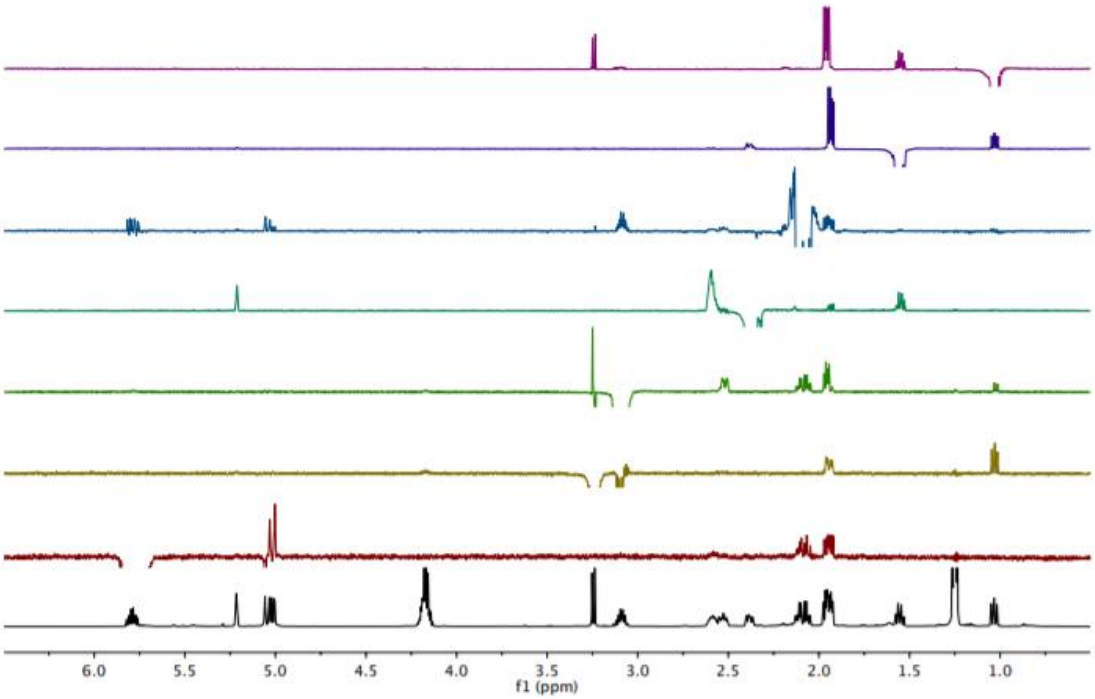


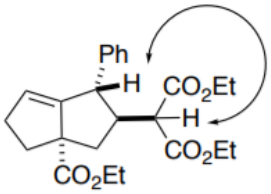




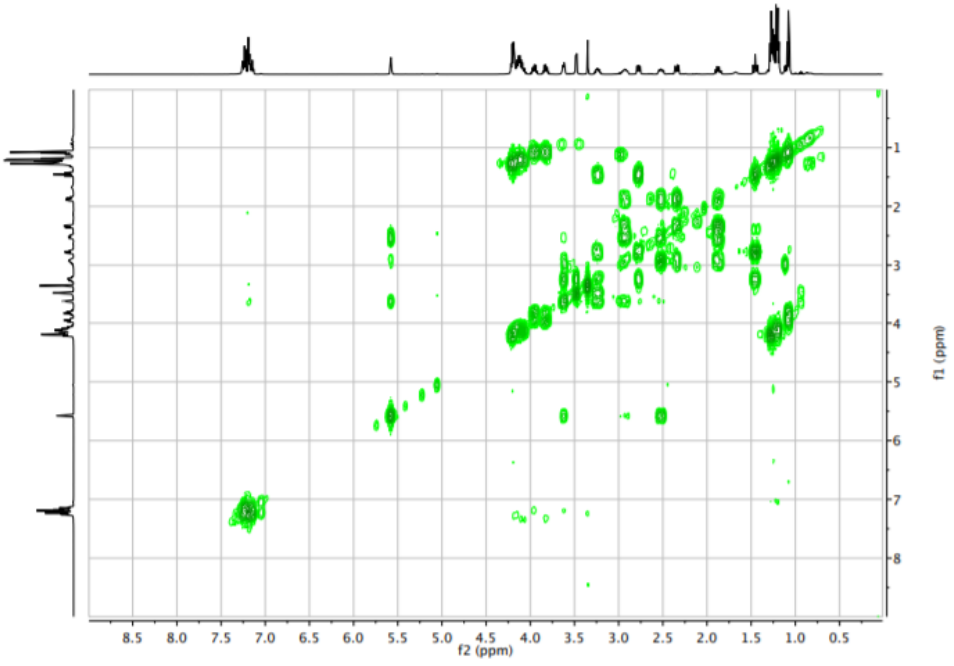
2-7e

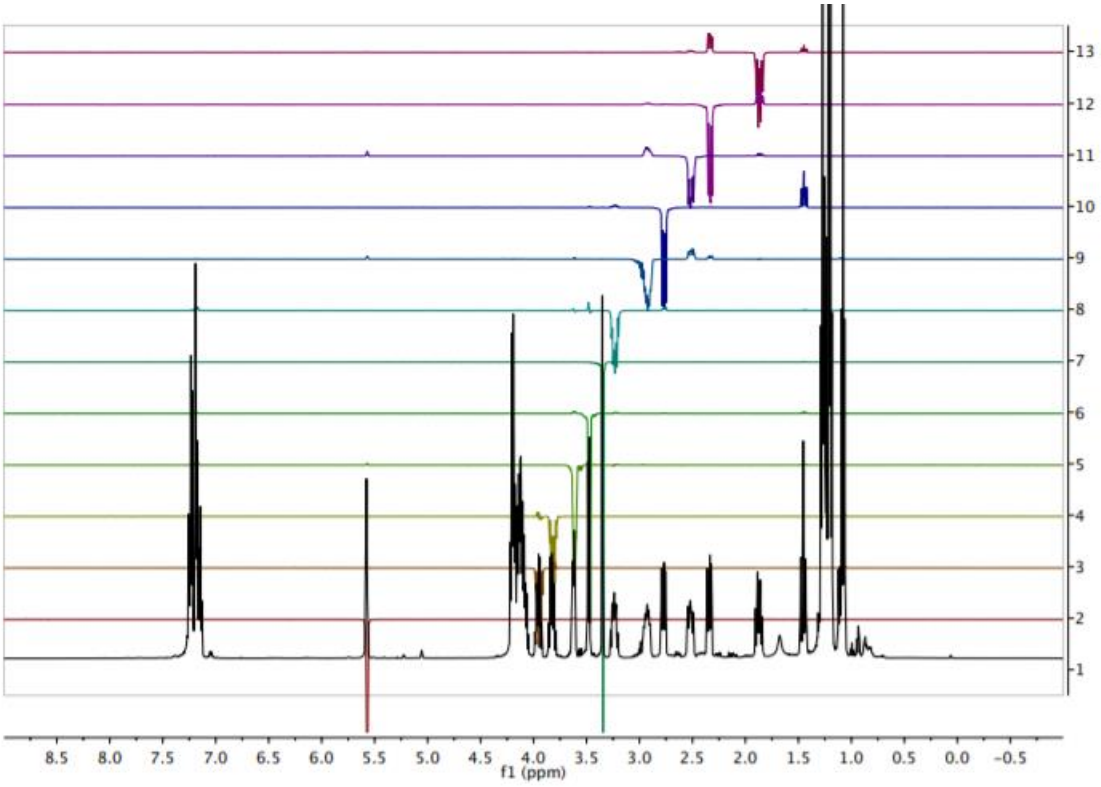


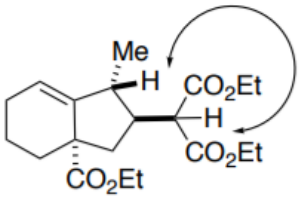




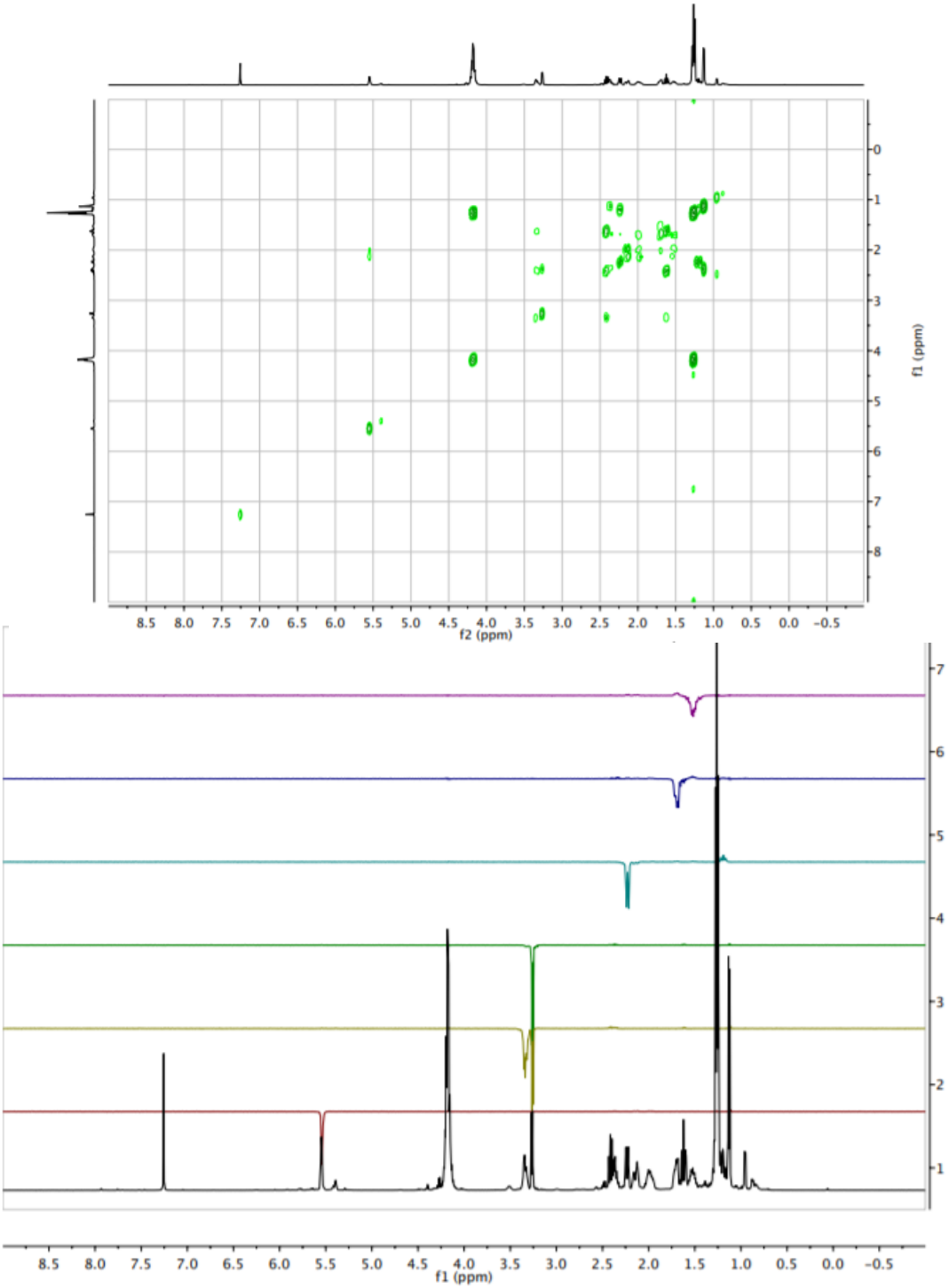
2-7p

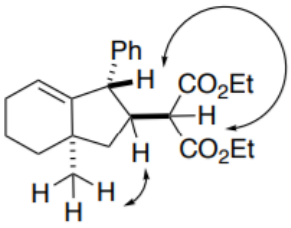




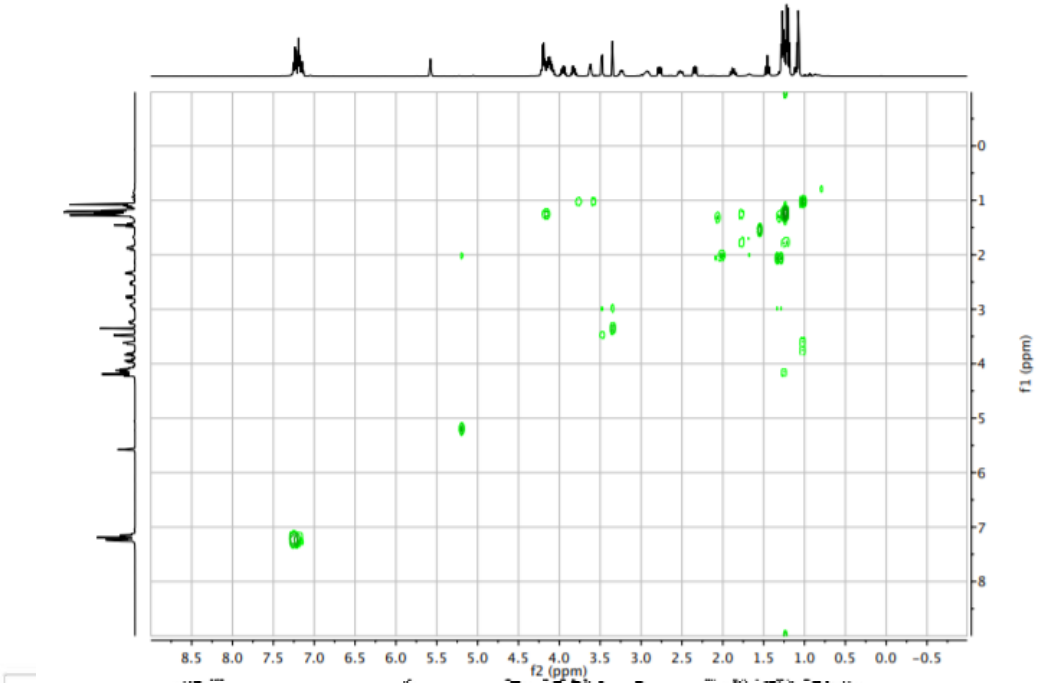


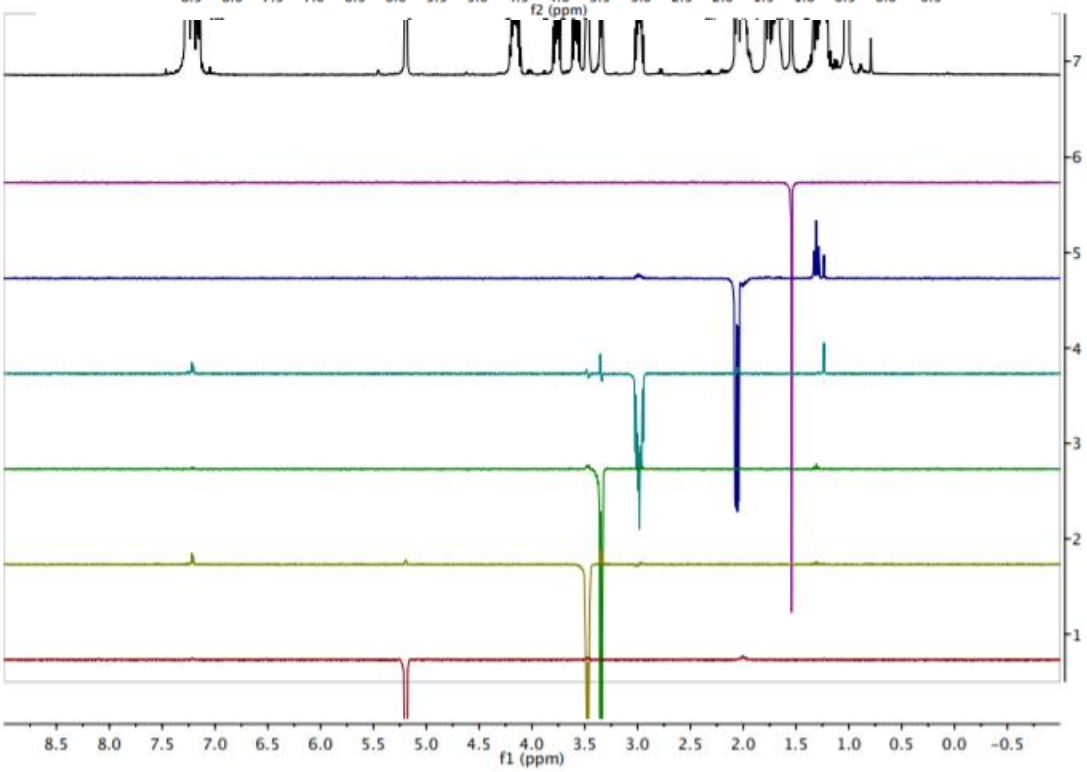
2-7k

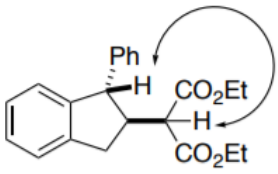




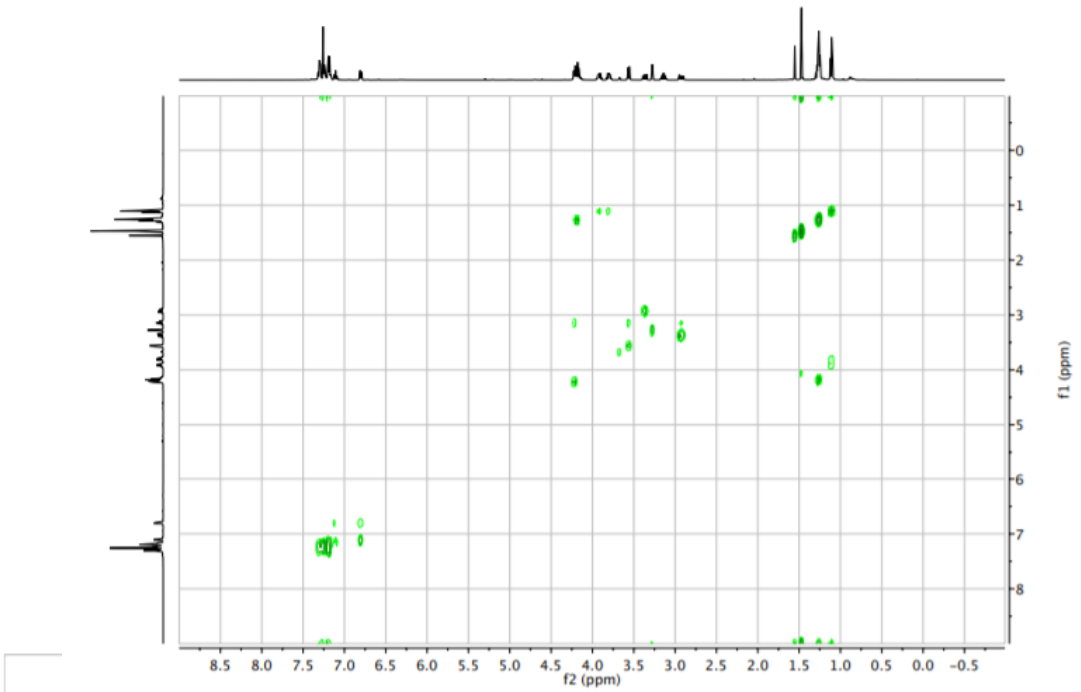
2-7o

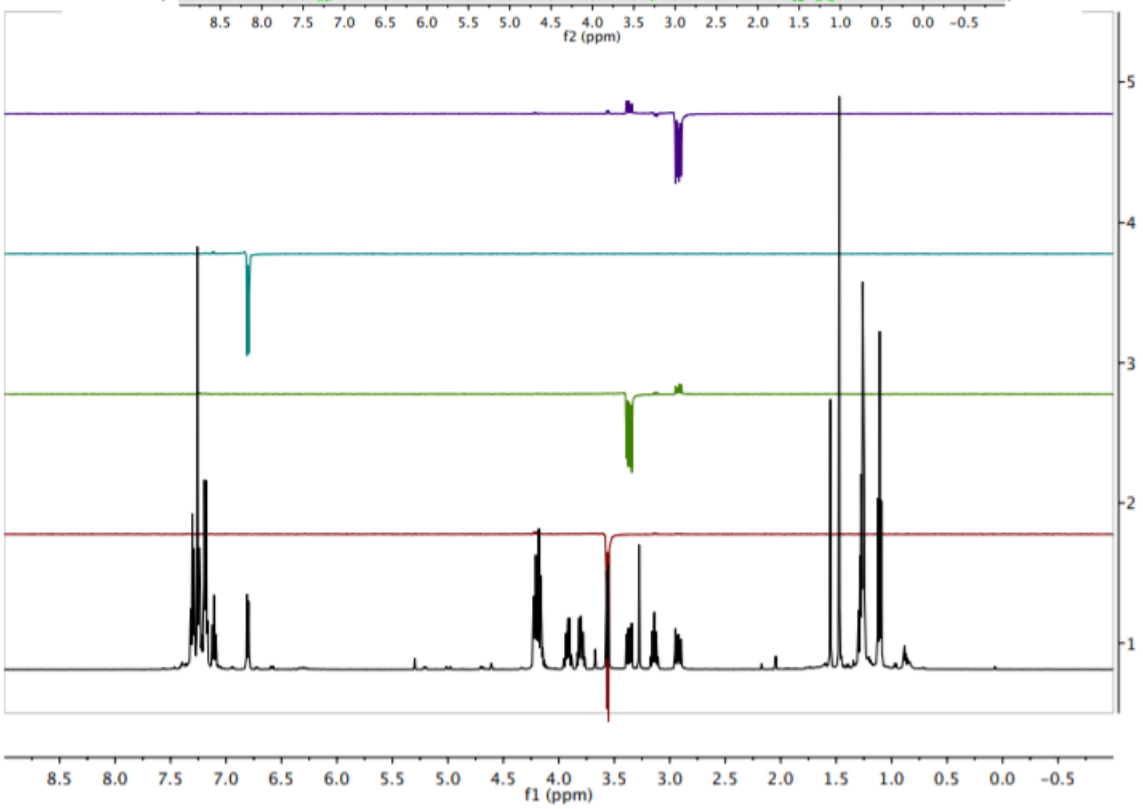


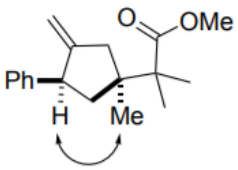




2-6e







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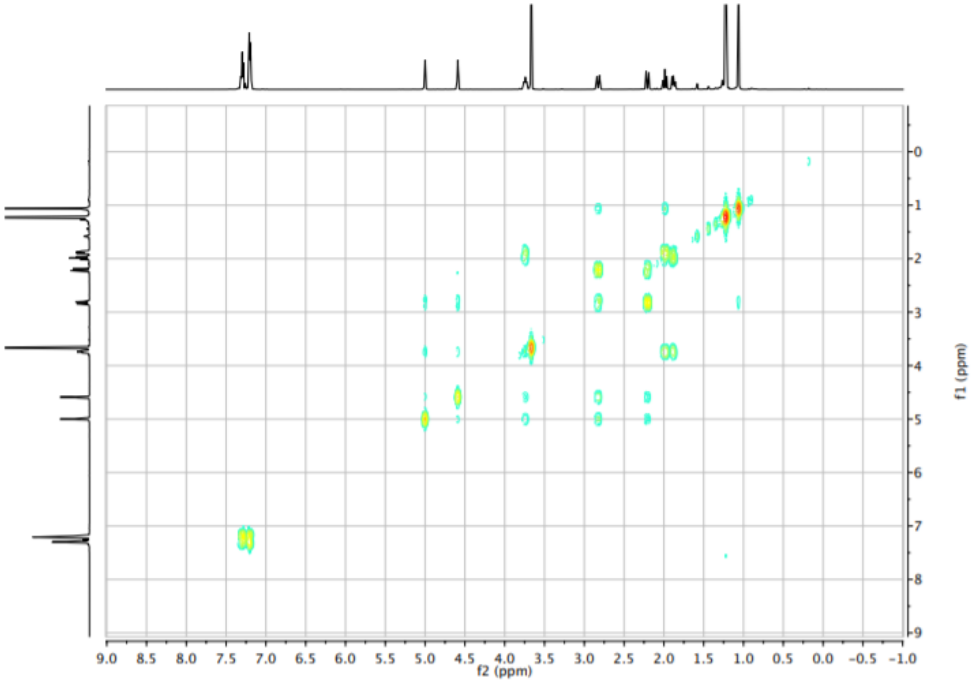

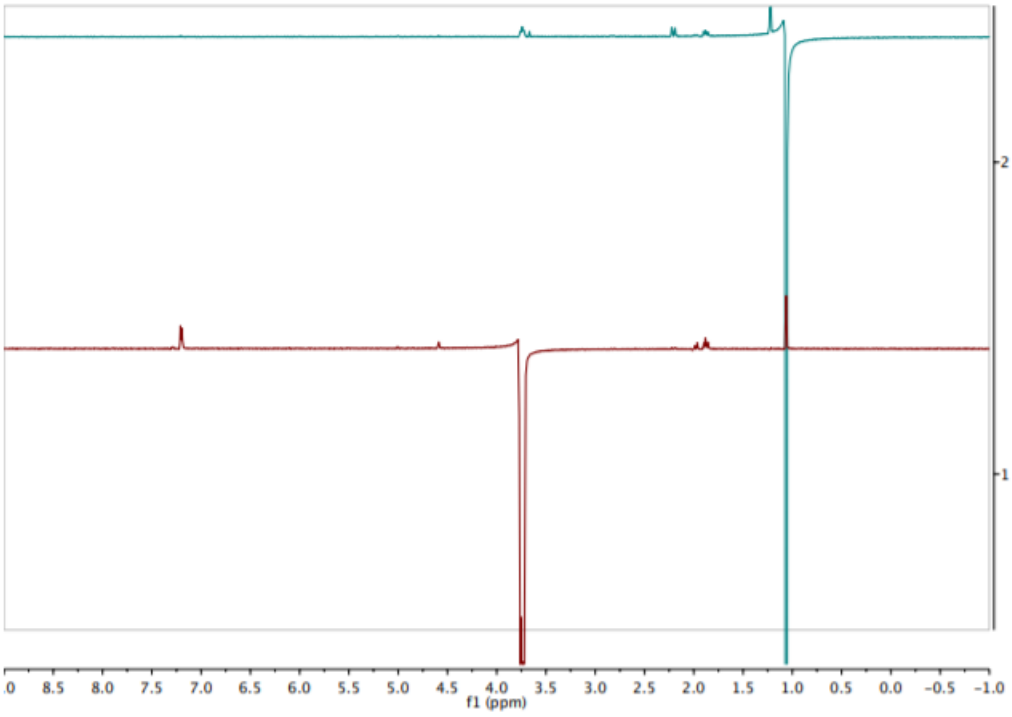

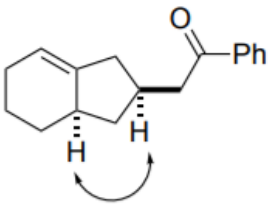

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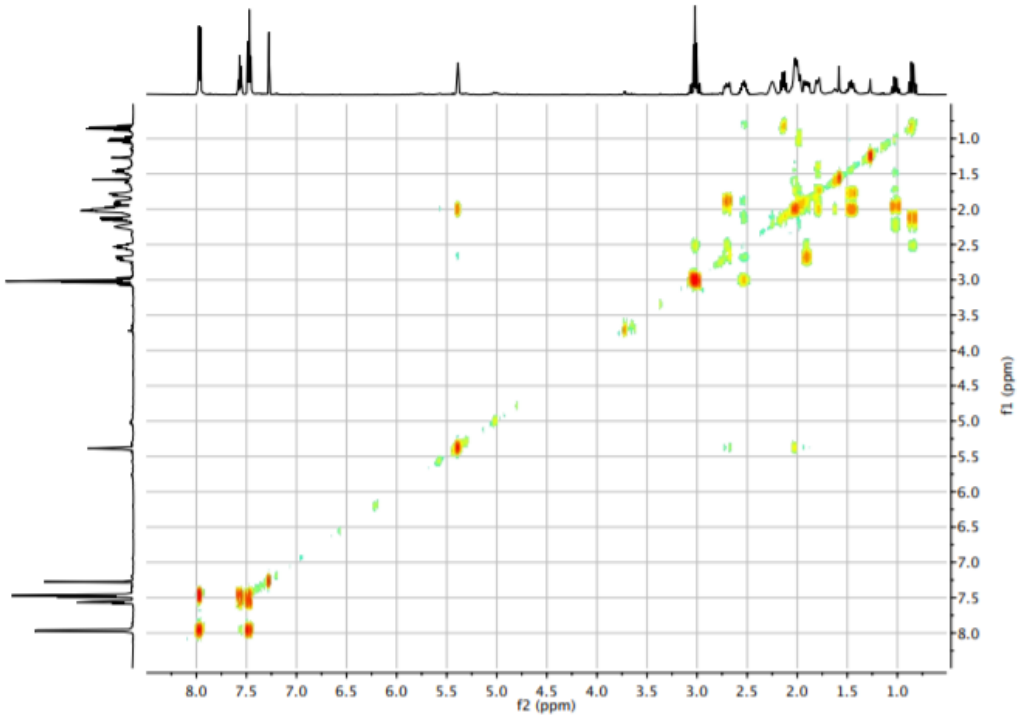
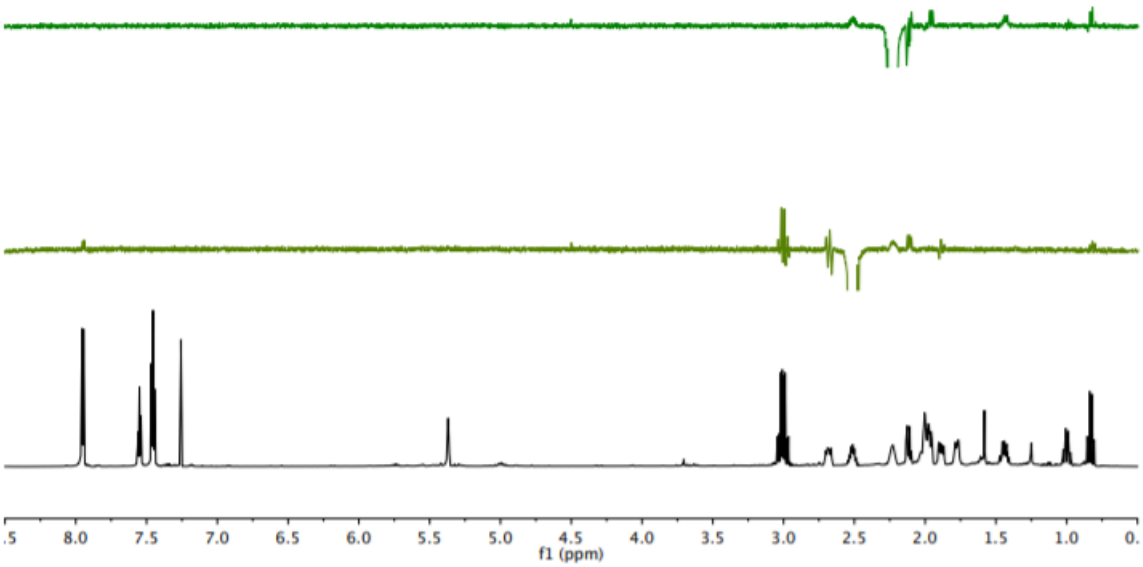
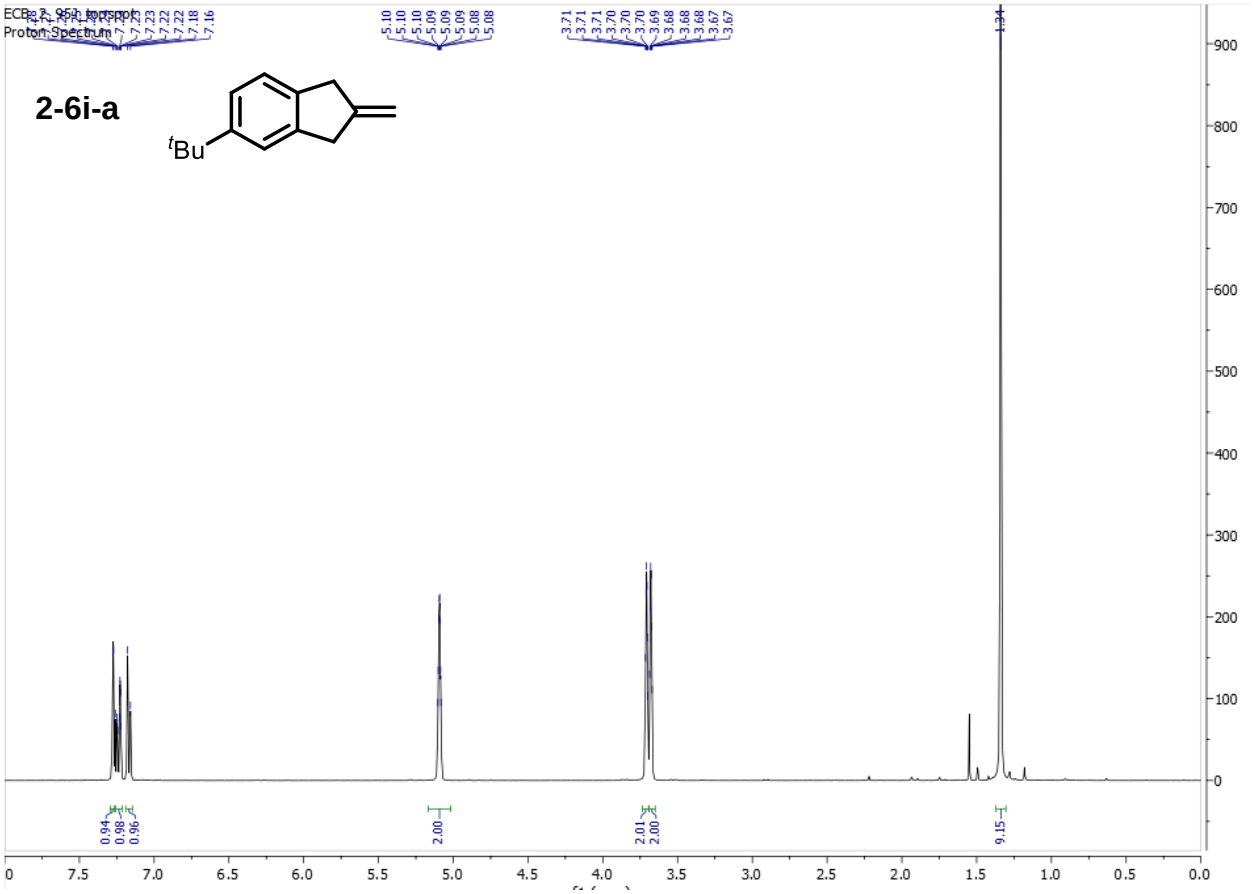




2.14 Unpublished Spectra



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(17) Fused cyclopentane products such as **2-14i** were quite sensitive to acid-mediated isomerization of the double bond, to the point that $CDCl_3$ could not be used as an NMR solvent without leading to some isomerization of the product. As such, NMR data for these compounds were collected in C_6D_6.

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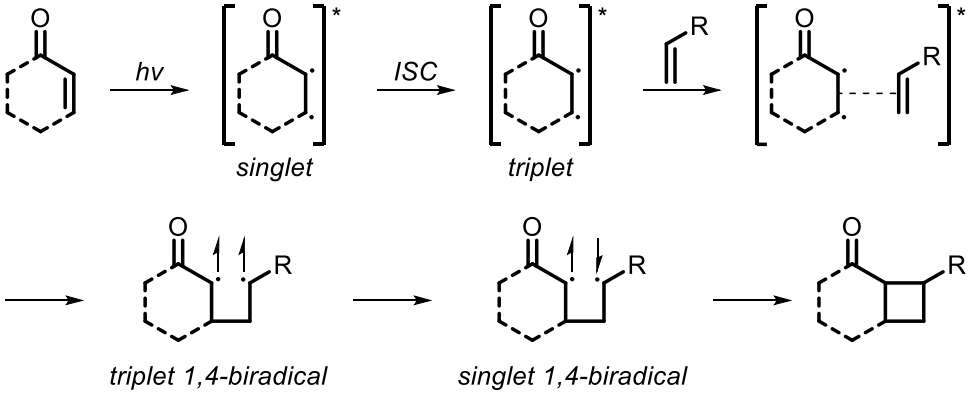
Chapter 3

Regiodivergent Palladium-Catalyzed Alkene Difunctionalization Reactions for the Construction of Methylene Cyclobutanes and Methylene Cyclopentanes

3.1 Introduction to the Synthesis of Cyclobutanes

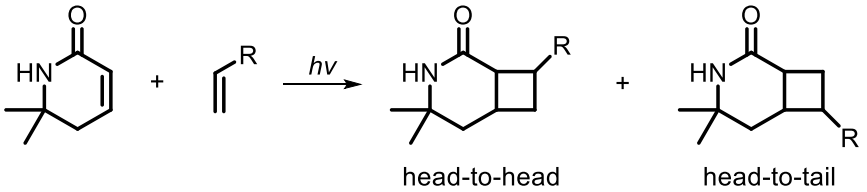
The most common method to construct cyclobutanes is, without doubt, the [2+2] cycloaddition of olefins.[1] The [2+2] cyclization is facilitated in several different ways; notably, photochemically with an activated alkene,[1,2,3] thermodynamically with a catalyst,[1c,4] and photochemically with a catalyst.[5] As shown in **Scheme 3-1**, a general

Scheme 3-1: [2+2] Photocycloaddition



mechanism representing a [2+2] photocycloaddition can be demonstrated in the cyclization of an enone with an unactivated olefin. First, the activated olefin is excited into a short-lived singlet state which degrades by intersystem crossing (ISC) to the triplet state. The triplet state reacts with the ground state of the unactivated alkene to form a triplet 1,4 biradical. The triplet biradical undergoes spin inversion to the singlet biradical thus allowing for the formation of the desired cyclobutane. The photocycloaddition has the potential to generate two different regiomers (**Table 3-1**) which are called the head-to-head and head-to-tail products. Typically, head-to-head products are observed when

Table 3-1: [2+2] Photocycloaddition head-to-head and head-to-tail electronic trends

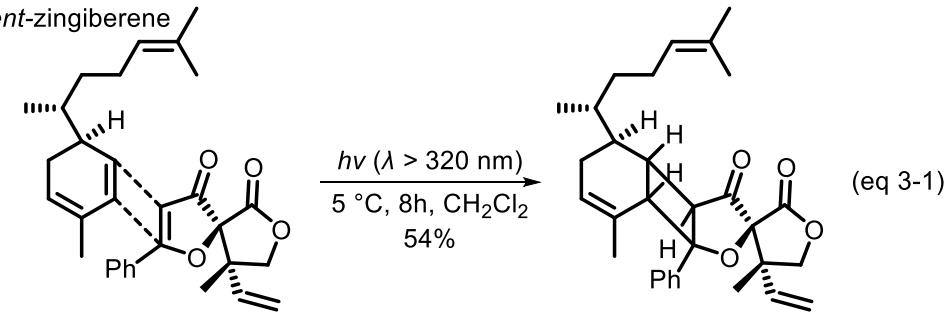


R	HH:HT
CN	82:18
OEt	5:95

the R group on the alkene is electron-withdrawing and head-to-tail products when the R group is electron-donating.[6,7] The application of [2+2] photocycloadditions have been used to good effect in the synthesis of natural products containing cyclobutane motifs.

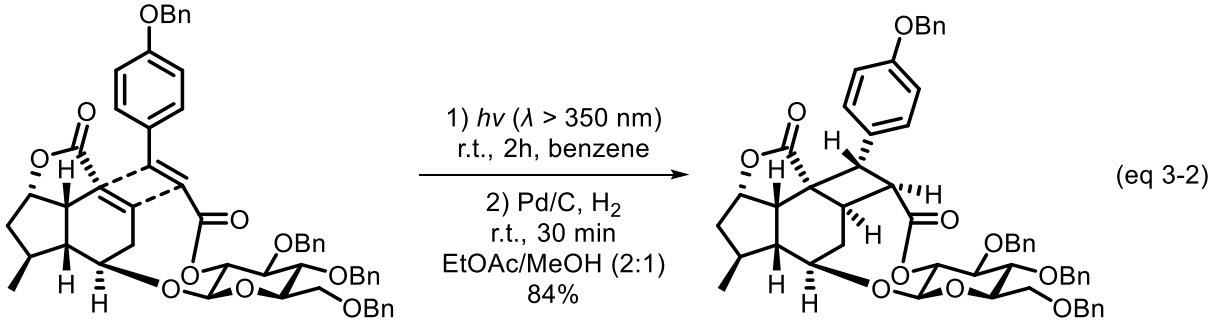
Nicolaou 2007 [8]

ent-zingiberene



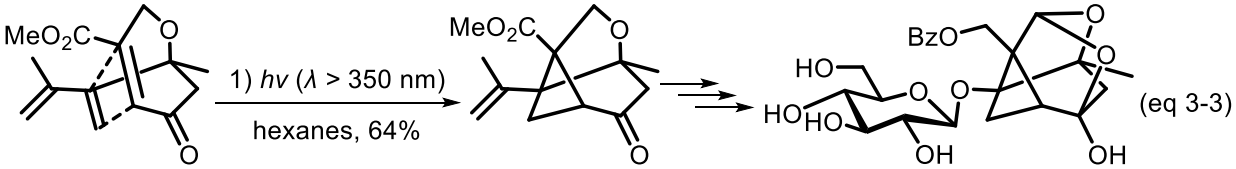
hyperolactone C (-)-biyouyanagin A (eq 3-1)

Mangion 2005 [9]



(-)-littoralisone (eq 3-2)

Hatakeyama 1994 [10]

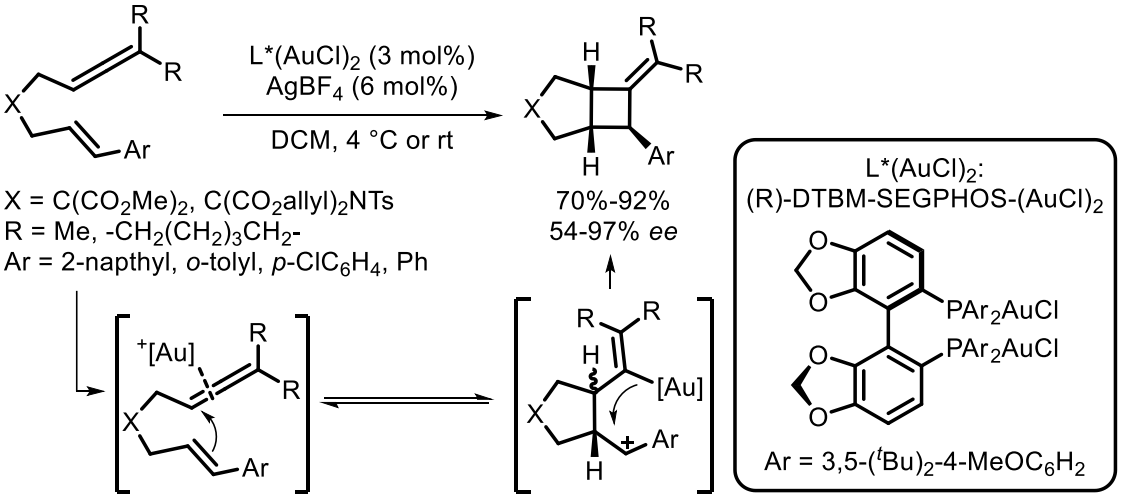


(-)-paeoniflorin (eq 3-3)

Selected examples include, Nicolaou and coworkers used a [2+2] photocycloaddition between *ent*-zingiberene and hyperolactone C to synthesize (-)-biyouyanagin A in 54% yield (eq 3-1).[8] Mangion and coworkers employed an intramolecular [2+2] photocycloaddition followed by a global deprotection to construct (-)-littoralisone (eq 3-2).[9] Hatakeyama and coworkers also utilized an intramolecular [2+2] photocycloaddition to form a crucial cyclobutane intermediate that, upon further transformations, would form (-)-paeoniflorin (eq 3-3).[10]

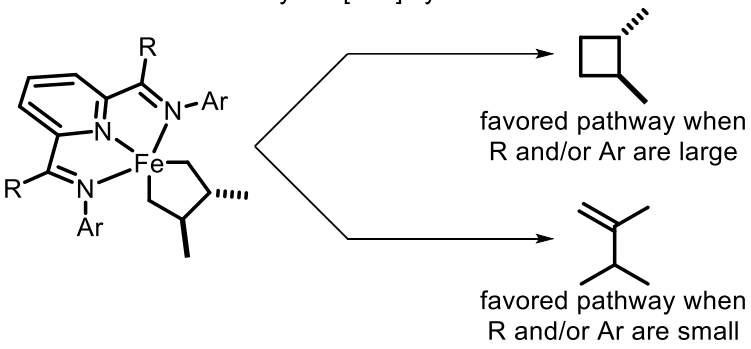
The activation energy that would normally be prohibitive for a thermal [2+2] cyclization can be lowered to accessible levels via a catalyst. In 2007, the Toste group reported the first gold-catalyzed cycloisomerization of allenes to alkylidene-cyclobutanes (**Scheme 3-2).** The proposed mechanism is a nucleophilic cascade cyclization that starts as the alkene attacks the allene producing a vinyl-gold species. This species in turn can attack the carbocation forming the 5,4- bicycle. An axially chiral ligand can be employed to allow up to 97% *ee* of the *cis*-formed product.[4a,11] Excitingly, in 2015, Hoyt and coworkers reported an iron-catalyzed intermolecular [2+2] cycloaddition of unactivated alkenes. This work was groundbreaking as for the first time, Hoyt and coworkers reported catalyst

Scheme 3-2: Gold-catalyzed nucleophilic cascade cyclization of allenes



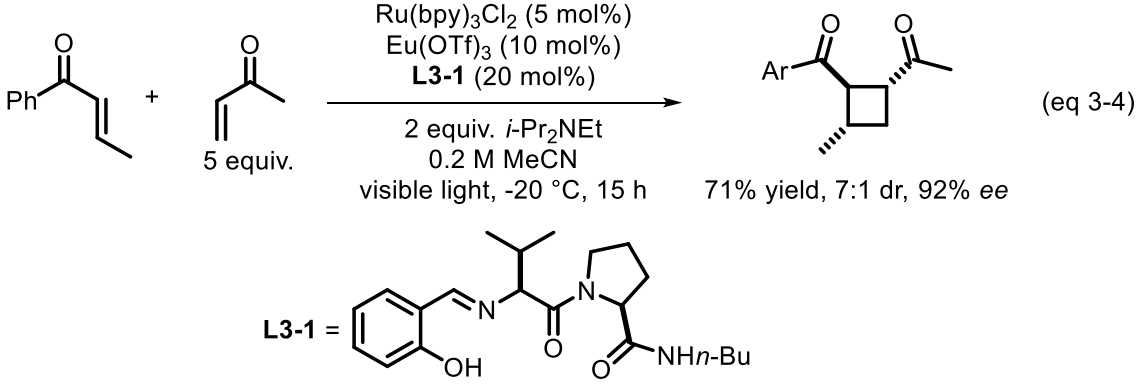
conditions to thermally dimerize small, unactivited alkenes for the construction of simple cyclobutanes. The products of the iron-catalysis are ligand dependent and can result in up to 98% yield of the desired cyclobutane products. As detailed in **Scheme 3-3**, the meso cyclobutane product can be favored when R and aryl substituents are bulky, giving more reductive elimination. The authors observe undesired beta-hydride elimination products when R and aryl groups are relatively smaller.[4b]

Scheme 3-3: Iron-catalyzed [2+2] cyclization



Thermal catalytic [2+2] cycloadditions have had success installing stereostereocenters in cyclobutane products; however, outside of conformationally appropriate, intramolecular cyclizations, photocycloadditions have not had the same success in exhibiting stereochemical control as their thermal counterparts. Du and coworkers recently reported a duel catalytic system in an approach to enantioselective [2+2] photocyclizations. As shown in eq 3-4, utilizing a Ruthenium-catalyst and a chiral

Du 2014 [5b]



ligand cocatalyst (**L3-1**), Du and coworkers were able to impart 92% enantiomeric excess into their cyclobutane products.[5b]

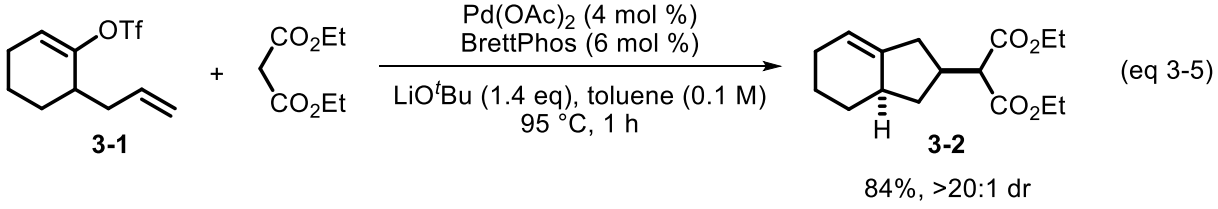
3.2 Introduction to Pd-Catalyzed Synthesis of Cyclobutanes

Over the past 15-20 years, Palladium-catalyzed alkene difunctionalization reactions have emerged as powerful tools for the construction of heterocycles and carbocycles.[12] As described in Chapters 1 and 2, our group has recently reported a series of Palladium—catalyzed alkene difunctionalization reactions for the synthesis of functionalized methylene cyclopentanes.[13,14] In general, these transformations form carbocycles in good yield and diastereoselectivity through the coupling of 1,5-dienes bearing triflate groups at C2 with exogenous amine, alcohol/phenol, indole, or stabilized carbanion nucleophiles. For example, treatment of **3-1** with diethyl malonate in the presence of $Pd(OAc)_2$, BrettPhos, and LiO^tBu afforded **3-2** in 84% yield with >20:1 dr (eq 3-5). These transformations are also effective for the formation of monocyclic products, such as the conversion of **3-3** with methyl isobutyrate to afford **3-4** (52%, >20:1 dr, eq 3-6). In our early work, with one exception in which 2-allylphenyltriflate underwent reaction with 3-methylindole to afford a benzocyclobutane derivative in 23% yield,[13b] all of these transformations provided exclusively 5-membered ring products through endo-cyclization reactions.

Given the generally high selectivity for 5-endo-cyclization, we were quite surprised to find that the coupling of gem-diester substrate **3-5a** with di-*tert*-butyl malonate under standard conditions afforded an inseparable 1:4 mixture of regioisomers **3-6a** and **3-7a** in 53% yield with only modest (1:4 selectivity) for the cyclopentane product (eq 3-7). In addition, we were quite excited to find this surprising reactivity given the utility of

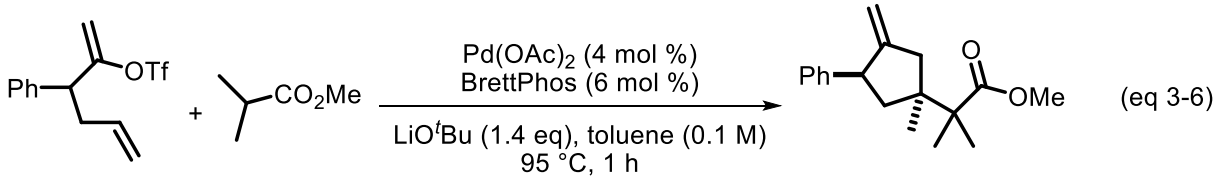
cyclobutanes and the challenges associated with their synthesis.[1-11] In this chapter we describe our studies on this system, which have led to the development of conditions for the regioselective and regiodivergent formation of either 4-membered or 5-membered ring products from a single starting material, along with mechanistic experiments that shine light on the mechanism for cyclobutene formation, which appears to involve a rare sp^3-sp^3 C-C bond-forming reductive elimination of a malonate from Pd(II).

Previous work



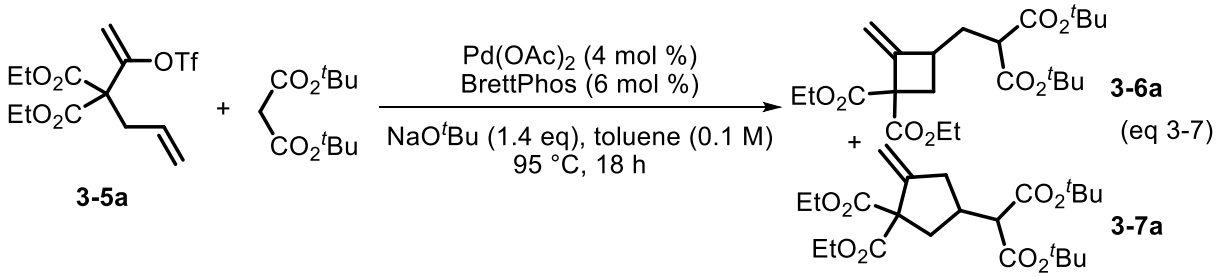
3-1 **3-2** (eq 3-5)

84%, >20:1 dr



3-3 **3-4** (eq 3-6)

52%, >20:1 dr



3-5a **3-6a** + **3-7a** (eq 3-7)

53%, 1:4 rr

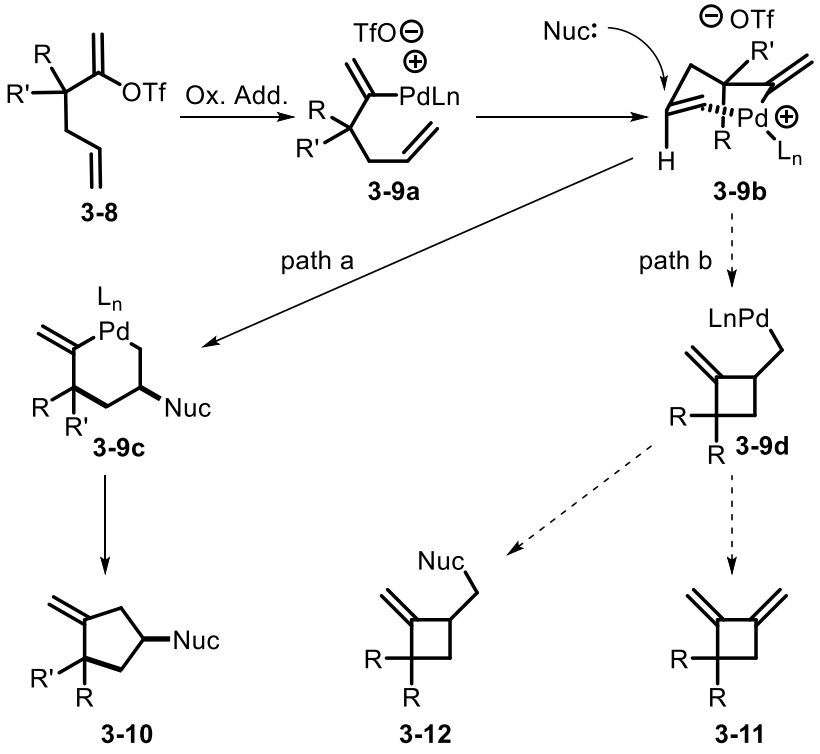
The work described in this chapter is comprised of both the author's (ECB), Jim Shepich III's (JS3), and Paige Maire Carpenter's (PMC) contributions. JS3 conducted reactions with a pyrrolidine nucleophile (eq 3-12) and assisted with substrate synthesis (**3-5b**). PMC conducted reactions with ethyl acetoacetate (eq 3-10 and eq 3-11) and

assisted with substrate synthesis (**3-5a**). We have decided to include JS3's and PMC's results in this dissertation to give the reader the full story about this transformation.

3.3 Optimization of Conditions for Selective Formation of Methylene Cyclopentane or Cyclobutane products

In our preliminary studies, we elected to take a two-pronged approach to optimization that involved an initial mechanistic experiment to generate a working hypothesis, followed by rational ligand screening to optimize conditions. Our previous studies suggested the formation of the cyclopentane product likely occurs as illustrated in **Scheme 3-4**. The reaction is presumably initiated by oxidative addition of the alkenyl triflate **3-8** to a Pd(0) complex generated by ligation and reduction of the Pd(II) precatalyst. Intermediate **3-9a** is then positioned to have the olefin bind to the Pd(II) center (**3-9b**), activating it for attack by the malonate nucleophile in an *anti*-carbopalladation of the alkene (path a). The resulting palladacycle (**3-9c**) then undergoes reductive elimination to liberate the 5-exo

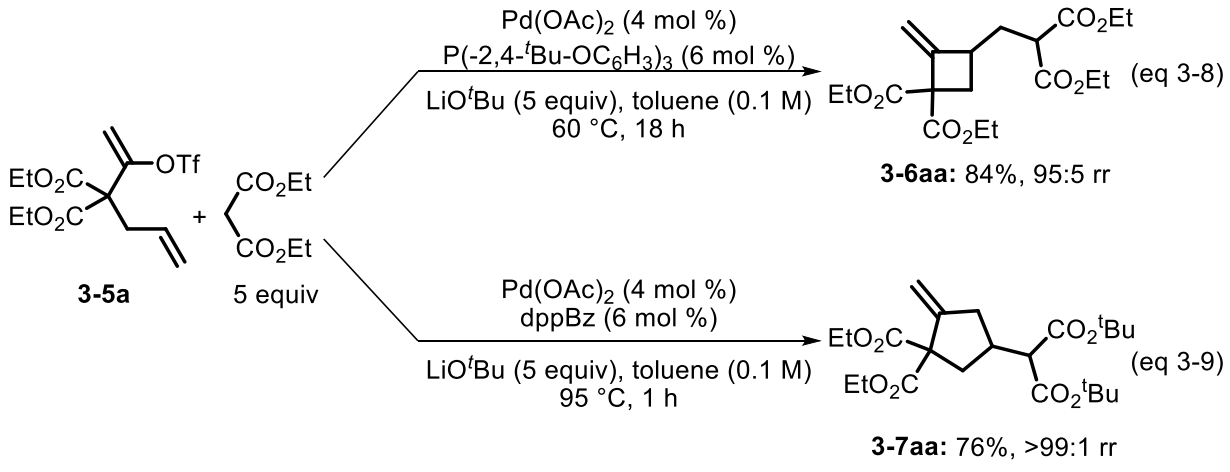
Scheme 3-4: Hypothesized mechanisms



product (**3-10**) and regenerate the Pd(0) catalyst. For path b, after the initial oxidative addition, **3-9b** could undergo a 1,2 migratory insertion that is facilitated by a Thorpe-Ingold effect from the alpha geminal substituents of the vinyl triflate substrate to form intermediate **3-9d**. Intermediate **3-9d** could either undergo beta-hydride elimination to form product **3-11** or be trapped by a nucleophile to give product **3-12**.

Given that 4-exo-migratory insertion processes are known to occur in Pd-catalyzed Heck reactions that afford cyclobutene products,[15] it seemed plausible that the methylene cyclobutane products could arise from migratory insertion followed by trapping by the nucleophile. As such, we carried out a simple control experiment in which the nucleophile was omitted with substrate **3-5a**. This reaction afforded from the reaction afforded the intramolecular Heck product, diene **3-11a**, in approximately 51% NMR yield.[16] This result is consistent the hypothesis outlined above, and with Mulzer's prior studies on intramolecular Heck reactions of related substrates.[15]

Based on this hypothesis, it seemed that use of bidentate ligands should favor the formation of the 5-exo product, as migratory insertion reactions are known to proceed most rapidly when monodentate ligands are employed.[17] After some screening, we found that use of bidentate ligands with small bite angles led to good regioselectivity for the 5-



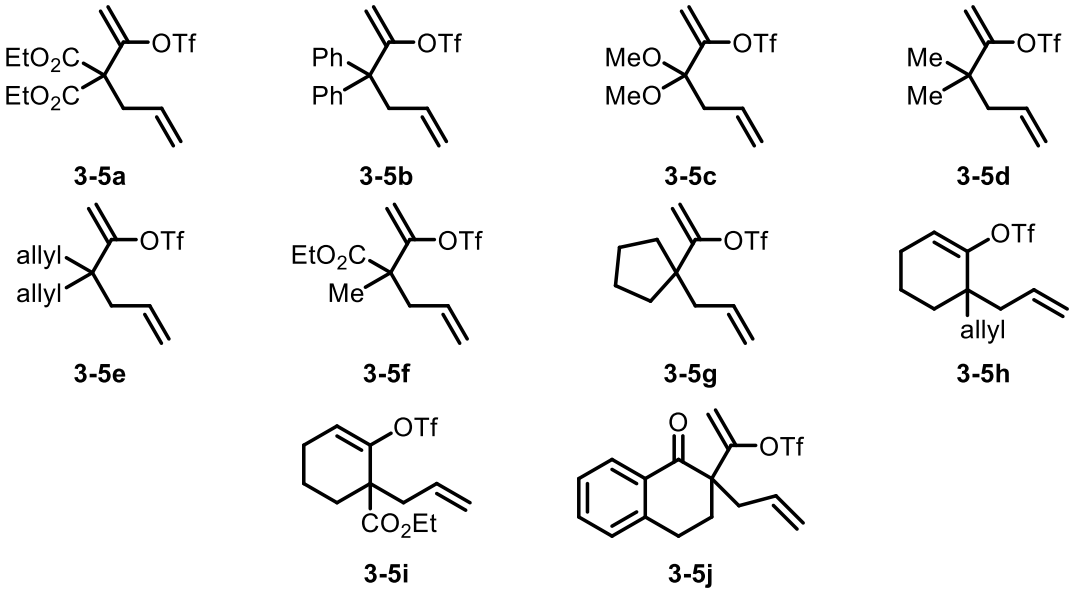
exo product, **3-7aa**, and 1,2-Bis(diphenylphosphino)benzene (dppBz) was selected as the optimal ligand (eq 3-9). Additionally, use of five equivalents of nucleophile increased both the regioselectivity and the chemical yield in these transformations.

In contrast, labile, monodentate ligands should accelerate the migratory insertion step,[17] and therefore lead to increased selectivity for the four-membered ring product. In general, a number of different monodentate ligands proved reasonable selectivities for the methylene cyclobutane product **3-6aa**. However, tris(2,4-di-*tert*-butylphenyl)phosphite provided the best isolated yields and regioselectivities. Further optimization, by increasing the amount of nucleophile to 5 equiv, and decreasing the temperature to 60°C, increased the overall isolated yield of the reactions, and also led to cleaner reactions, which greatly simplified the isolation of the desired products (eq 3-8). Further efforts to optimize conditions by changing the solvent, base, or palladium source had deleterious effects on yield and selectivity for the 4-exo product.

3.4 Substrates Employed in Pd-Catalyzed Alkene Difunctionalization Study

With conditions in hand for selective formation of either regioisomeric product, we turned our attention to exploring the scope of the reaction using a series of different alkenyl triflate derivatives. Substrates for these studies are shown in **Scheme 3-5**, and were prepared in 2-5 steps in most cases through formation and alkylation of the corresponding methyl ketone enolate, followed by enol triflate formation.

Scheme 3-5: Alkenyl substrates for palladium reactions

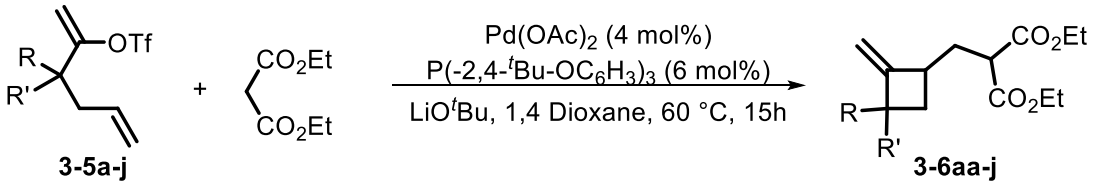


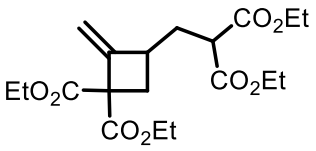
3.5 Scope of Methylene Cyclobutanes

As shown in **Scheme 3-6**, substrate **3-5b** gave excellent selectivity for the 4-exo product **3-6b**. However, utilizing smaller substituents (**3-6d**, **3-6g**, **3-6h**) the selectivity for the cyclobutane regioisomer is diminished, which suggests the Thorpe-Ingold effect plays a significant role in the cyclobutane-forming reactions. In addition, the fact that gem-diester substrate **3-5a** is transformed in much higher regioselectivity than gem-dimethyl substrate **3-5d** indicates that electronic effects also influence the regioselectivty. Acetal-bearing substrate **3-5c** was smoothly transformed to **3-6c** in excellent regioselectivity and good chemical yield. In contrast to other examples, in this case the cyclobutane **3-6c** was

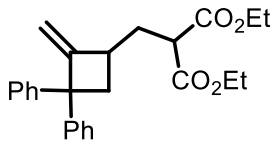
easily separable from its cyclopentane regioisomer **3-7c**.[18] Substrates **5g-j** were efficiently transformed to spirocyclic products (**3-6g**, **3-6j**) or bicyclic products (**3-6h**, **3-6i**) in good yield, but with moderate regioselectivity.

Scheme 3-6: Scope of methylene cyclobutanes[a,b,c]

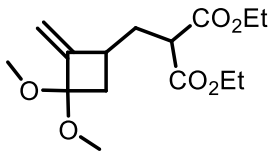




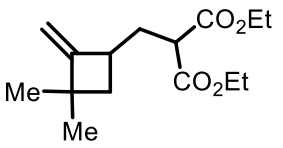
3-6aa: 84%, 95:5 rr



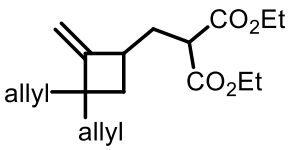
3-6b: 74%, >99:1 rr



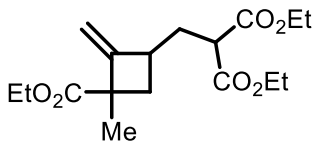
3-6c: 72%, 100:0 rr



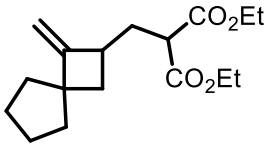
3-6d: 86%, 60:40 rr



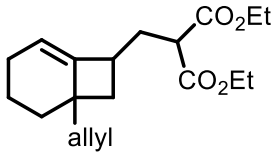
3-6e: 80%, 75:25 rr



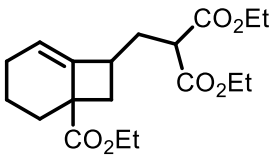
3-6f: 86%, 73:27 rr
75:25 dr



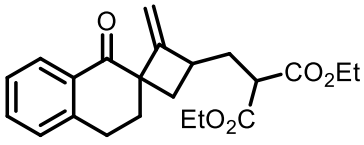
3-6g: 83%, 60:40 rr



3-6h: 89%, 50:50 rr



3-6i: 78%, 75:25 rr



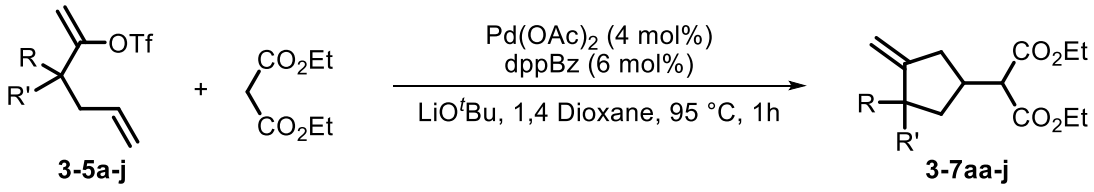
3-6j: 82%, 75:25 rr

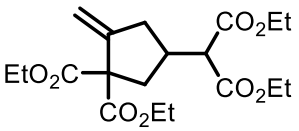
[a]Conditions: 1.0 equiv substrate, 5.0 equiv diethyl malonate, 5 equiv LiO^{t}Bu, 4 mol% $Pd(OAc)_2$, 6 mol% P-(2,4-^{t}BuO$C_6H_3)_3$, 1,4 dioxane (0.1M), 60 °C, 15 h. [b]Yields are isolated yield averages of two or more experiemnts. [c]Regioisomeric ratios and diasteromeric ratios were determined by ^{1}H NMR analysis.

3.6 Scope of Methylene Cyclopentanes

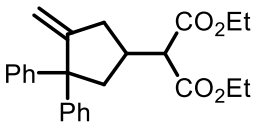
The conditions re-optimized for formation of methylene cyclopentane products were also examined in reactions of **3-5a-j**, and we were pleased to see high regioselectivity for

Scheme 3-7: Scope of methylene cyclopentanes[a,b,c]

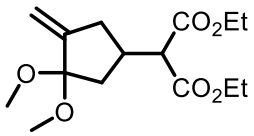




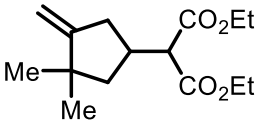
3-7aa: 76%, >99:1 rr



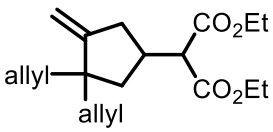
3-7b: 71%, 77:23 rr[d]



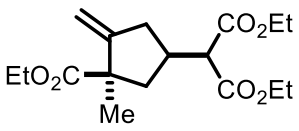
3-7c: 84%, 100:0 rr



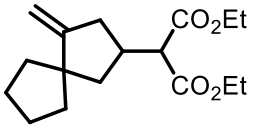
3-7d: 72%, >99:1 rr



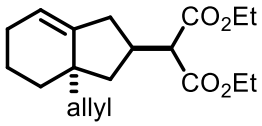
3-7e: 79%, >99:1 rr



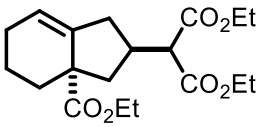
3-7f: 72%, >99:1 rr
67:33 dr



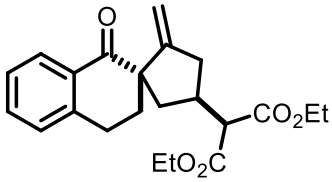
3-7g: 80%, >99:1 rr



3-7h: 94%, >99:1 rr
93:7 dr



3-7i: 80%, >99:1 rr[e]
75:25 dr (separable)

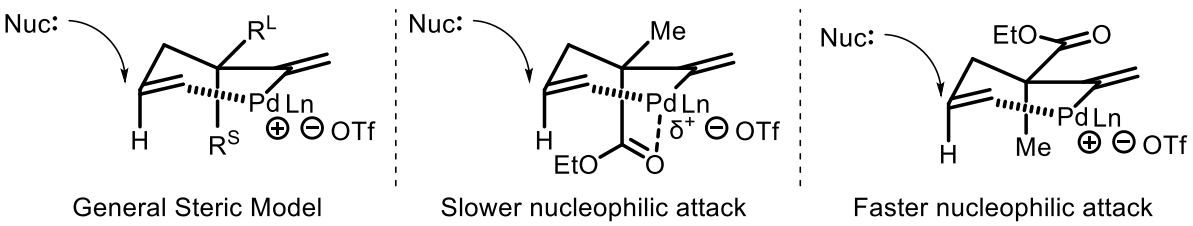


3-7j: 84%, >99:1 rr[e]
75:25 dr (separable)

[a]Conditions: 1.0 equiv substrate, 5.0 equiv diethyl malonate, 5 equiv LiO^{t}Bu, 4 mol% $Pd(OAc)_2$, 6 mol% dppBz, 1,4 dioxane (0.1M), 95 °C, 1 h. [b]Yields are isolated yield averages of two or more experiemnts. [c]Regioisomeric ratios and diasteromeric ratios were determined by ^{1}H NMR analysis. [d]Conditions: 1.0 equiv substrate, 2.0 equiv diethyl malonate, 2.0 equiv NaO^{t}Bu, 4 mol% $Pd(OAc)_2$, 6 mol% dppBz, Toluene (0.1M), 95 °C, 15 h. [e]Reaction was conducted for 15 h.

the 5-exo product in all cases except for **3-7b** (**Scheme 3-7**, 77:23 rr). This further illustrates the dramatic impact of the Thorpe-Ingold effect on product regiochemistry. In contrast to the cyclobutene-forming reactions, in which regiochemistry decreased with smaller alpha substituents, this was not observed in five-membered ring-forming reactions. Unfortunately, the excellent diastereoselectivity (typically >20:1 in most cases) we observed with Brettphos under our original conditions[14] was diminished when dppBz was employed (**3-7f**; **3-7h**–**3-7j**). However, the diastereomers are separable by careful column chromatography. Functional group tolerance in these reactions was unaffected by ligand choice, and esters, alkenes, and acetals were tolerated under either set of conditions.[18] Products **3-7h**–**3-7j** gave the expected major diastereomer based on our previous observations and predictive model; however, product **3-7f** gave the opposite of the expected diastereoselectivity. As shown in **Scheme 3-8**, We hypothesis substrate **3-5f** is uniquely situated to be able to provide additional stabilization of the palladium complex by donating electrons from the carbonyl to the metal center. The increased electron density reduces the cationic nature of palladium and reduces the rate of nucleophilic attack on the coordinated alkene. Although substrate **3-5j** is similar to **3-5f** in the electronics of geminal R functional groups, product **3-7j** yields the expected diastereomer, opposite of the observed in **3-7f**. We believe product **3-7j** follows our stereochemical model because the steric effects of the tetralone ring outweigh the

Scheme 3-8: Proposed origin of diastereoselectivity observed in product **3-7f**

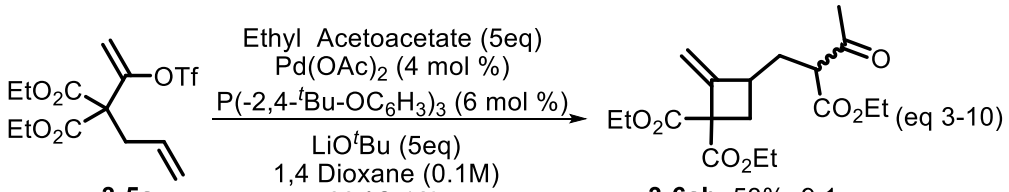


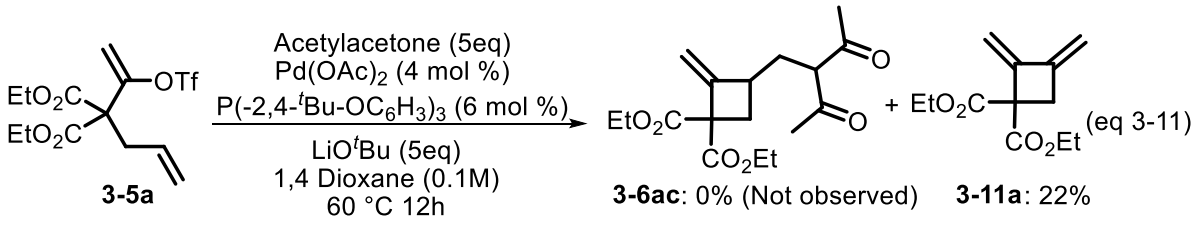
General Steric Model | Slower nucleophilic attack | Faster nucleophilic attack

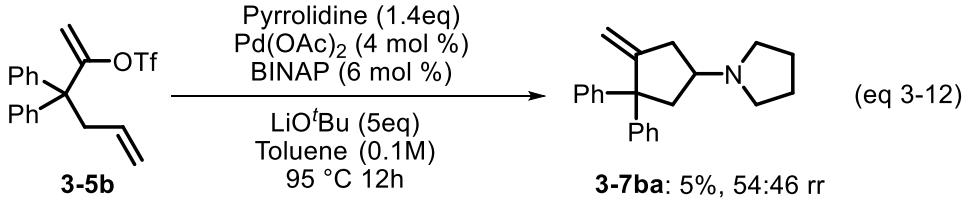
electron donation effects of the carbonyl. However, it should be noted both diastereoselectivies are modest with **3-7f** formed with 2:1 dr and **3-7j** generated with 3:1 dr.

3.7 Scope of Additional Nucleophiles

We also briefly explored the reactivity of other nucleophiles in these transformations (Scheme 3). The reaction of ethyl acetoacetate was less effective than diethyl malonate, providing a 53% yield of **3-6ab** with a 9:1 regioselectivity (eq 3-10). However, efforts to form the methylene cyclopentane regioisomer utilizing ethyl acetoacetate as the nucleophile were unsuccessful. Use of acetylacetone as the nucleophile was also unsuccessful under both four- and five-membered ring forming conditions. However, the beta hydride elimination product, **3-11a**, was isolated in 22% yield with the bulky phosphite ligand (eq 3-11). However, we were pleased to find that **3-5b** did undergo coupling with pyrrolidine in low yield to afford a 5% isolated yield of a 54:46 mixture of





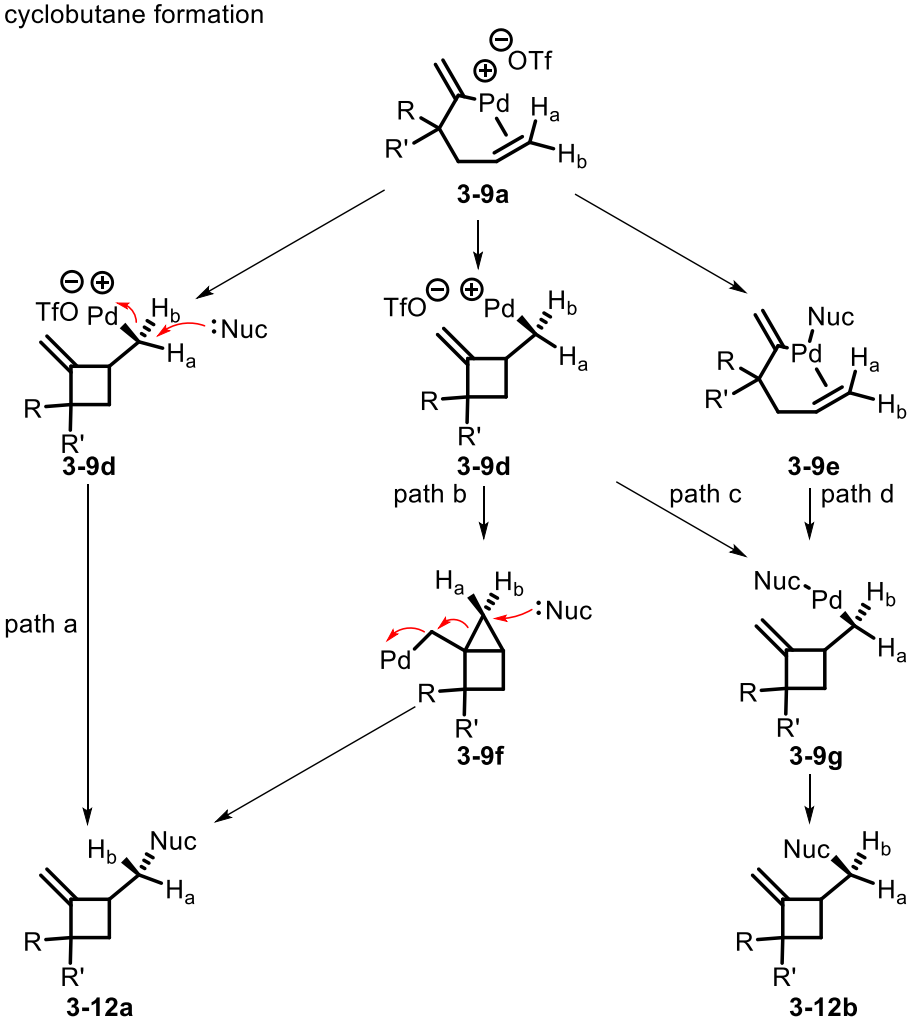


product regioisomers. Thus, although additional optimization will clearly be needed to further expand the scope of this chemistry, it appears that the cyclobutene-forming reactions are not strictly limited to malonate nucleophiles. Further optimization of reaction conditions with nitrogen nucleophiles will be detailed in Chapter 4.

3.8 Proposed Reaction Mechanism and Stereochemistry

Given the unusual, regiodivergent reactivity in this system, we sought to examine the mechanism of formation of the methylene cyclobutane regioisomer. Our preliminary studies described above suggested that cyclobutane formation occurred via migratory insertion of the alkene into the Pd-C bond after oxidative addition of the triflate group.

Scheme 3-9: Possible mechanisic pathways for methylene cyclobutane formation

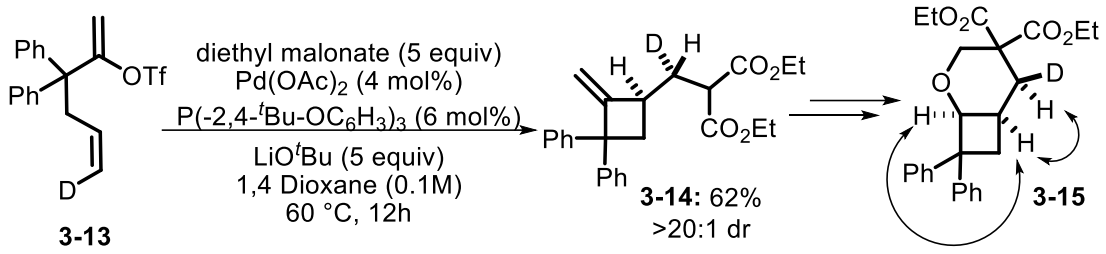


However, four different pathways could potentially lead to the observed product (**Scheme 3-9**). Two pathways (a and b) involve initial 1,2-migratory insertion from **3-9a** to **3-9d**.[17] Intermediate **3-9d** could then undergo a formal S_N2-reductive elimination with the malonate anion to afford the product (path a). Alternatively, **3-9d** could undergo 3-exo migratory insertion into the exocyclic alkene to form bicyclo[2.1.0]pentane intermediate **3-9f**. The bicycle can then be transformed to product **3-12a** through S_N2'-like reductive elimination with the nucleophile.[19]

Two other pathways (c and d) would involve reductive elimination from the metal, rather than outer-sphere S_N2 substitution. Intermediate **3-9d** could undergo transmetallation with the nucleophile to afford **3-9g** (path c), which could then undergo C–C bond-forming reductive elimination to provide **3-12b**. Finally, intermediate **3-9g** could also be generated by transmetallation of **3-9a** with the malonate anion to provide **3-9e**, followed by subsequent migratory insertion (path d). Given the fact that paths a and b should involve reductive elimination with inversion of configuration at the carbon bound to palladium to afford **3-12a**, whereas paths c and d should proceed via stereoretentive reductive elimination to give stereoisomeric product **3-12b**, it seemed possible to differentiate these pathways through stereochemical labeling.

In order to examine the stereochemical outcome of this reaction, we elected to prepare a deuterated version of substrate **3-5b**, as that substrate showed the highest inherent selectivity for generation of the methylene cyclobutane regioisomer. As such, *Z*-deuterioalkene substrate **3-13** was prepared and subjected to our standard conditions.

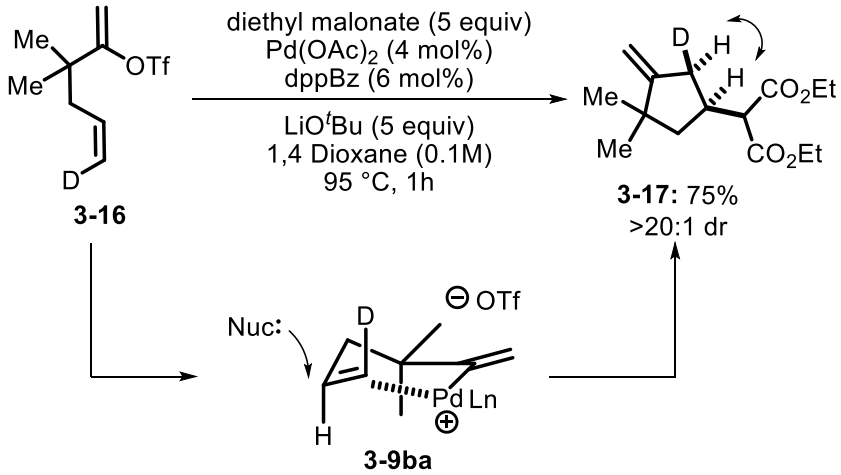
Scheme 3-10: Stereochemical outcome - cyclobutanes



Product **3-14** was generated in 62% yield as a single stereoisomer (>20:1 dr). The stereochemistry was then determined through multi-step conversion of **3-14** to **3-15**, the stereochemistry of which was assigned by ^{1}H NMR nOe experiments (**Scheme 3-10**). To the best of our knowledge, this is the first example of sp3-sp3 C-C bond-forming reductive elimination from Pd(II) involving a malonate nucleophile.[20] Although this experiment has shed considerable light on the mechanism of these reactions, it remains unclear whether the malonate binds to the palladium(II) complex before (path d) or after (path c) the migratory insertion step.

Finally, to provide support for our hypothesis that the 5-membered ring forming reactions still proceed through our previously reported mechanism (**Scheme 3-4**), despite the use of the chelating ligand, we examined the reaction of Z-deuterio alkene **3-16**. As shown in **Scheme 3-11**, when **3-16** was treated with diethyl malonate under standard

Scheme 3-11: Stereochemical outcome - cyclopentanes



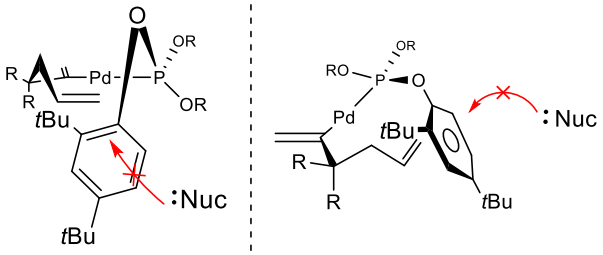
conditions, **3-17** was formed in 75% yield with >20:1 dr (**Scheme 3-11**). The observed product stereoisomer is consistent with our prior observations[13,14] that indicate the cyclopentane products are generated through nucleophilic attack of the malonate onto the coordinated alkene in intermediate **3-9ba**.

3.9 Explanation of Ligand Effects

Regardless of whether the reaction proceeds via path c or path d, our observed ligand effects are also consistent with our mechanistic hypothesis. Migratory insertion reactions are known to proceed most rapidly with coordinatively unsaturated, cationic palladium complexes. The fact that the chelating bis-phosphine ligand dbbBz provides high selectivity for 5-membered ring formation is likely due to the fact that migratory insertion will be slower in an L_2Pd complex that contains a chelating phosphine, rather than a labile, monodentate ligand.

The efficiency of the bulky phosphite ligand at promoting selective 4-exo carbopalladation may be due to two different factors working simultaneously. First, the phosphite is relatively electron poor and labile, which likely accelerates the crucial migratory insertion step. In addition, as shown in **Scheme 3-12**, the phosphite ligand, which has bulky *tert*-butyl groups at that extend quite far from the metal center may also sterically shield the face of the coordinated olefin from attack by an exogenous

Scheme 3-12: Suggested ligand effects blocking nucleophilic attack (left-viewed as if face on, right-viewed as if side on)



nucleophile in a manner similar to that of some ligands used for asymmetric additions to allylpalladium complexes.

3.10 Conclusion

In conclusion, we have developed two complementary catalyst systems to target for either the methylene cyclobutane or methylene cyclopentane regioisomer. Larger geminal substituents and electron withdrawing groups alpha to the vinyl triflate favor the methylene cyclobutane formation. The methylene cyclopentane regioisomer is formed via an exogenous nucleophilic attack of the coordinated olefin followed by reductive elimination off the metal center. The methylene cyclobutane regioisomer is formed via a *syn*-1,2-migratory insertion followed by reductive elimination off the metal center. To our knowledge this is the first example of a sp3-sp3 carbon-carbon coupling with a malonate.

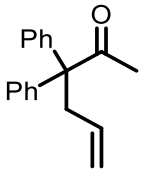
The work in this chapter is currently being prepared for publication.

3.11 Experimental

General Considerations: All reactions were carried out under a nitrogen atmosphere in vacuum and flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The substrates **3-5a**,[13c] **3-5d**,[13d] **3-5e**,[13d] **3-5g**,[13c] and N-(2-pyridyl)triflimide[21] were prepared by previously published methods. Alkenyl triflate starting materials were stored in a freezer under nitrogen. Bulk quantities of cesium carbonate, lithium *tert*-butoxide, and lithium hexamethyldisilazide were stored in nitrogen-filled glove box and small amounts were removed within a few days of use. Toluene, tetrahydrofuran, dichloromethane, and diethyl ether were purified using a GlassContour solvent purification system. Anhydrous 1,4 dioxane was purchased from Sigma-Aldrich and was used without purification. Structural and stereochemical assignments were made on the

basis of 2-D COSY and nOe experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in **Schemes 3-6** and **3-7** and equations 3–10 and 3-11 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown **Schemes 3-6** and **3-7** and equations 3–10 and 3-1.

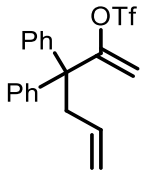
Preparation and Characterization of Substrates



3,3-diphenylhex-5-en-2-one (3-S1) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with sodium hydride (95%, 7.53 mmol, 181 mg, 1.1 equiv). 1,1 diphenyl acetone (6.85 mmol, 1.44 g, 1 equiv) was dissolved in DMF (7 mL, 1 M) and added to the flask. The reaction was stirred at rt for 10 min until the bubbles stopped. Allyl bromide (8.22 mmol, 710 µL, 1.2 equiv) was added to the flask and the reaction heated to 80 °C with stirring for 15 h. The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (15 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the

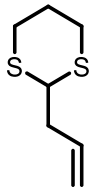
eluent. This procedure afforded 1.317 g (77%) of the title compound as a yellow-white semisolid, mp 61-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4 H) 7.28–7.20 (m, 6 H) 5.60–5.44 (m, 1 H) 4.92–4.79 (m, 2 H) 3.07 (d, *J* = 7.1 Hz, 2 H) 2.04 (s, 3 H).



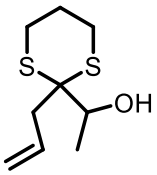
3,3-diphenylhexa-1,5-dien-2-yl trifluoromethanesulfonate (3-5b) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (5.9 mmol, 1.2 g, 1.2 equiv) dissolved in THF (12 mL, 0.5 M). The reaction flask was cooled to -78 °C. **3,3-diphenylhex-5-en-2-one (3-S1)** (4.9 mmol, 1.23 g, 1 equiv) was dissolved in THF (10 mL, 0.5 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (5.4 mmol, 1.93 g, 1.1 equiv) was dissolved in THF (11 mL, 0.5 M) and added to the reaction while at -78 °C. The reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (15 mL) and stirred briefly. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 98.5:1:0.5 hexanes: ethyl acetate: triethyl amine as the eluent. This procedure afforded 1.48 g (79%) of the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.24 (m, 10 H) 5.65–5.53 (m, 1 H) 5.43 (d, *J* = 4.6 Hz, 1 H) 5.19 (d, *J* = 4.6 Hz, 1 H) 5.13–4.97 (m, 2 H) 3.18 (d, *J* = 6.7 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.79, 141.34, 133.72, 129.03, 128.11, 127.25, 118.49, 118.08 (t, J_{CF} = 321 Hz), 104.40, 56.95, 42.93; IR (film) 3060, 3021, 1650, 1599, 1495, 1429, 1418 cm^{-1}; HRMS (EI 70 eV) m/z: [M] calcd for $C_{19}H_{17}F_3O_3S$ 382.0850; found 382.0 and 341.0 [M–allyl radical] and 41.0 [allyl radical].



2-allyl-1,3-dithiane (3-S2) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 1,3 dithiane (30 mmol, 3.61 g, 1 equiv) dissolved in THF (30 mL, 1 M). The flask was cooled to 0 °C and nBuLi (33 mmol, 2.5 M in hex, 13.2 mL, 1.1 equiv) was added dropwise. The reaction was stirred for 4 hours at 0 °C then cooled to -78 °C. Allyl bromide (33 mmol, 2.9 mL, 1.1 equiv) was added dropwise added to the flask. The reaction was stirred for 20 min at -78 °C. The reaction was warmed to rt and allowed to stir over night (15 h). The mixture was quenched with aqueous ammonium chloride (50 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified distillation (130 °C with reduced pressure). This procedure afforded 4.13 g (86%) of the title compound as a yellow oil.

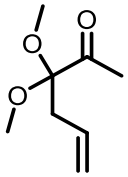
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.1, 10.0, 7.0 Hz, 1 H) 5.21–5.07 (m, 2 H) 4.10 (t, *J* = 6.9 Hz, 1 H) 2.94–2.78 (m, 4 H) 2.55–2.48 (m, 2 H) 2.12 (dtt, *J* = 14.5, 4.8, 2.7 Hz, 1 H) 1.93–1.79 (m, 1 H).



1-(2-allyl-1,3-dithian-2-yl)ethan-1-ol (3-S3) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **2-allyl-1,3-dithiane (3-S2)** (25.7 mmol, 4.13 g, 1 equiv) dissolved in THF (26 mL, 1 M). The flask was cooled to 0 °C and nBuLi (28.3 mmol, 2.5 M in hex, 11.3 mL, 1.1 equiv) was added dropwise. The reaction was stirred for 2 hours at 0 °C then cooled to -78 °C. Freshly distilled acetaldehyde (28.3 mmol, 1.6 mL, 1.1 equiv) was added dropwise added to the flask. The reaction was stirred for 20 min at -78 °C. The reaction was warmed to rt and allowed to stir over night (15 h). The mixture was quenched with aqueous ammonium chloride (50 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 3.23 g (62%) of the title compound as a yellow oil and recovered 0.70 g (17%) of unreacted starting material.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08–5.96 (m, 1 H) 5.20–5.10 (m, 2 H) 4.26 (qd, *J* = 6.3, 2.1 Hz, 1 H) 3.03–2.93 (m, 2 H) 2.72 (s, 1 H) 2.70–2.60 (m, 3 H) 2.44 (ddt, *J* = 15.1, 7.0, 1.5

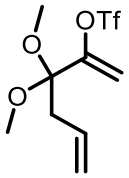
Hz, 1 H) 2.12–2.00 (m, 1 H) 1.85 (dtt, *J* = 14.5, 11.2, 3.4 Hz, 1 H) 1.38 (d, *J* = 6.3 Hz, 3 H).



3,3-dimethoxyhex-5-en-2-one (3-S4) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with N-chlorosuccinimide (13.3 mmol, 1.77 g, 4 equiv) and silver nitrate (13.3 mmol, 2.25 g, 4 equiv) dissolved in THF (15 mL, 0.9 M) and methanol (15 mL, 0.9 M). 2,6 lutidine (13.3 mmol, 1.75 mL, 4 equiv) was added to the flask. The flask was cooled to 0 °C and **1-(2-allyl-1,3-dithian-2-yl)ethan-1-ol (3-S3)** (3.3 mmol, 0.677, 1 equiv) dissolved in 1:1 THF:methanol (6 mL, 0.5 M) was added dropwise. The reaction was stirred for 10 minutes at 0 °C then warmed to rt and stirred for an additional 90 minutes. While the first reaction was stirring, another vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with oxalyl chloride (3.64 mmol, 350 µL, 1.1 equiv) dissolved in DCM (3 mL, 1 M). The reaction flask was cooled to -78 °C. Dimethyl sulfoxide (7.3 mmol, 550 µL, 2.2 equiv) was added dropwise to the flask. The reaction was stirred for 1 h at -78 °C. The first flask, after stirring for 90 minutes at rt, had the methanol removed under reduced pressure. Saturated aqueous sodium sulfite (15 mL), sodium carbonate (15 mL), brine (15 mL) and DCM (15 mL) were added to the reaction flask and the mixture was filtered through celite. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude oil was dissolved in a minimal amount of dry DCM (2 mL) and added to the second flask

(after the 1 hour stir at -78 °C). The reaction was stirred for 2 hours at -78 °C. Triethyl amine (16.6 mmol, 2.3 mL) was added to the second flask and allowed to stir for an additional 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (20 mL) and stirred for 5 minutes. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium carbonate, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:diethyl ether as the eluent. Due to the volatility of the title compound, some solvent remained after column. This procedure afforded 0.243 g (46%) of the title compound as a clear oil.

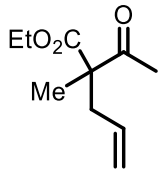
^{1}H NMR (401 MHz, $CDCl_3$) δ 5.68–5.53 (m, 1 H) 5.14–5.04 (m, 2 H) 3.26 (s, 6 H) 2.57 (d, *J* = 7.2 Hz, 2 H) 2.19 (s, 3 H).



3,3-dimethoxyhexa-1,5-dien-2-yl trifluoromethanesulfonate (3-5c) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (3.79 mmol, 756 mg, 1.2 equiv) dissolved in THF (4 mL, 0.9 M). The reaction flask was cooled to -78 °C. **3,3-dimethoxyhex-5-en-2-one (3-S4)** (3.16 mmol, 500 mg, 1 equiv) was dissolved in THF (3 mL 1 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (3.48 mmol, 1.25 g, 1.1 equiv) was dissolved in THF (4 mL, 0.8 M) and added to the reaction while at -78 °C. The reaction was stirred for

30 minutes at -78 °C. The reaction was warmed to rt and allowed to react for 4 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and stirred for 5 minutes. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 98: 2 hexanes: ethyl acetate as the eluent. This procedure afforded 690 mg (75%) of the title compound as a colorless oil.

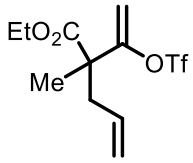
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65–5.54 (m, 1 H) 5.49 (dd, *J* = 3.6, 1.4 Hz, 1 H) 5.42 (dd, *J* = 3.6, 1.4 Hz, 1 H) 5.19–5.08 (m, 2 H) 3.24 (s, 6 H) 2.57 (dd, *J* = 7.1, 1.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.49, 130.70, 119.02, 118.27 (t, J_{CF} = 320 Hz), 107.36, 100.36, 49.07, 36.96; IR (film) 3082, 2949, 2840, 2157, 1662, 1645, 1418 cm^{-1}; HRMS (GC-APCI) m/z: [M] calcd for $C_9H_{13}F_3O_5S$ 290.0436; found 259.0256 [M–OCH_3]; HRMS (EI 70 eV) m/z: $[M]^+$ calcd for $C_9H_{13}F_3O_5S$ 290.0436; found 259.0256 [M–OCH_3] also 249.0 [M–allyl radical] and 41.0 [allyl radical].



Ethyl 2-acetyl-2-methylpent-4-enoate (3-S5) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium carbonate (22.5 mmol, 3.1 g, 1.5 equiv) and dry acetone (30 mL). Ethyl 2-methylacetoacetate (15 mmol, 2.12 mL, 1 equiv) was added to the flask. The reaction was stirred at rt for 10 minutes. Allyl bromide (22.5 mmol, 2 mL, 1.5 equiv) was added to the flask. The flask was equipped with a reflux condenser and refluxed at 70 °C overnight (15 h). The reaction

was cooled to rt, and the mixture was quenched with water (20 mL). The mixture was stirred briefly then transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 2.73 g (99%) of the title compound as a colorless oil.

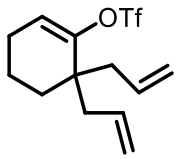
^{1}H NMR (401 MHz, $CDCl_3$) δ 5.71–5.55 (m, 1 H) 5.14–5.02 (m, 2 H) 4.17 (q, *J* = 7.1 Hz, 2 H) 2.61 (ddt, *J* = 14.1, 7.2, 1.3 Hz, 1 H) 2.48 (ddt, *J* = 14.1, 7.6, 1.3 Hz, 1 H) 2.13 (s, 3 H) 1.30 (s, 3 H) 1.24 (t, *J* = 7.1 Hz, 3 H).



Ethyl 2-methyl-2-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)pent-4-enoate (3-5f) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (12 mmol, 2.4 g, 1.2 equiv) dissolved in THF (12 mL, 1 M). The reaction flask was cooled to -78 °C. **Ethyl 2-acetyl-2-methylpent-4-enoate (3-S5)** (10 mmol, 1.84 g, 1 equiv) was dissolved in THF (10 mL, 1 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (11 mmol, 3.94 g, 1.1 equiv) was dissolved in THF (11 mL, 1 M) and added to the reaction while at -78 °C. The reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to rt and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (20 mL) and stirred briefly. The mixture was transferred to a separatory funnel. The aqueous layer was extracted

with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 98:2 hexanes: ethyl acetate as the eluent. This procedure afforded 2.40 g (76%) of the title compound as a yellow oil.

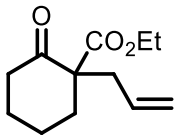
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.72—5.62 (m, 1 H) 5.30 (d, *J* = 4.7 Hz, 1 H) 5.18—5.13 (m, 2 H) 5.10 (d, *J* = 4.7 Hz, 1 H) 4.23—4.14 (m, 2 H) 2.59 (ddt, *J* = 14.0, 7.6, 1.1 Hz, 1 H) 2.53 (ddt, *J* = 13.9, 7.0, 1.2 Hz, 1 H) 1.38 (s, 3 H) 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.81, 156.73, 131.72, 119.79, 118.25 (q, J_{CF} = 320 Hz), 103.28, 61.85, 50.95, 39.73, 20.59, 13.86; IR (film) 2985, 1739, 1660, 1419 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{11}H_{15}O_5F_3S$ 317.0665; found 317.0667.



6,6-diallylcyclohex-1-en-1-yl trifluoromethanesulfonate (3-5h) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (12 mmol, 2.4 g, 1.2 equiv) dissolved in THF (12 mL, 1 M). The reaction flask was cooled to -78 °C. 2,2-diallylcyclohexan-1-one (10 mmol, 1.78 g, 1 equiv) was dissolved in THF (10 mL, 1 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (11 mmol, 3.94 g, 1.1 equiv) was dissolved in THF (11 mL, 1 M) and added to the reaction while at -78 °C. The reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to rt and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (20 mL) and stirred briefly.

The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 99:1 hexanes: ethyl acetate as the eluent. This procedure afforded 2.51 g (81%) of the title compound as a yellow oil.

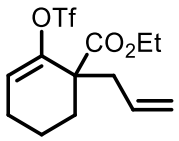
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.81 (t, *J* = 4.2 Hz, 1 H) 5.80–5.70 (m, 2 H) 5.14–5.03 (m, 4 H) 2.39–2.29 (m, 2 H) 2.20–2.11 (m, 4 H) 1.70–1.64 (m, 2 H) 1.64–1.59 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.45, 133.39, 118.59, 118.31 (q, J_{CF} = 320 Hz), 117.94, 41.55, 41.25, 31.19, 24.56, 18.00; IR (film) 3079, 2937, 2844, 1673, 1640, 1441, 1409 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{13}H_{17}O_3F_3S$ 311.0923; found 311.0908.



Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate (3-S6) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with sodium hydride (95%, 11 mmol, 264 mg, 1.1 equiv). Ethyl 2-oxocyclohexane-1-carboxylate (10 mmol, 1.6 mL, 1 equiv) was dissolved in DMF (10 mL, 1 M) and added to the flask. The reaction was stirred at rt for 10 min until the bubbles stopped. Allyl bromide (12 mmol, 1.1 mL, 1.2 equiv) was added to the flask and the reaction heated to 80 °C with stirring for 15 h. The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (20 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried

over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 2.09 g (99%) of the title compound as a colorless oil.

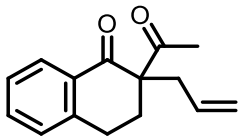
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81–5.66 (m, 1 H) 5.08–4.97 (m, 2 H) 4.18 (q, 2 H) 2.60 (dd, *J* = 13.9, 7.0 Hz, 1 H) 2.52–2.39 (m, 3 H) 2.33 (dd, *J* = 13.9, 7.8 Hz, 1 H) 2.02–1.94 (m, 1 H) 1.80–1.55 (m, 3 H) 1.45 (ddd, *J* = 13.7, 11.9, 4.5 Hz, 1 H) 1.24 (t, *J* = 7.1 Hz, 3 H).



Ethyl 1-allyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-2-ene-1-carboxylate (3-5i) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with diisopropyl amine (3.2 mmol, 0.45 mL, 1.2 equiv) dissolved in THF (3 mL, 1 M). The flask was cooled to 0 °C and nBuLi (3.14 mmol, 2.5 M in hex, 1.25 mL, 1.1 equiv) was added dropwise. The reaction was stirred for 20 minutes at 0 °C then cooled to -78 °C. **Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate (3-S6)** (2.85 mmol, 0.60 g, 1 equiv) dissolved in THF (3 mL, 1 M) was added dropwise added to the flask. The reaction was stirred for 20 min at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (3.14 mmol, 1.124 g, 1.1 equiv) was dissolved in THF (3 mL, 1 M) and added dropwise to the flask and the reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to rt and allowed to stir over night (15 h). The mixture was quenched with aqueous ammonium chloride (10 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered

and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes: ethyl acetate as the eluent. This procedure afforded 0.88 g (90%) of the title compound as a colorless oil.

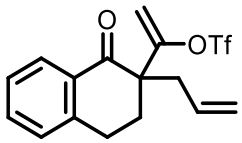
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 5.2, 3.0 Hz, 1 H) 5.76–5.67 (m, 1 H) 5.18–5.11 (m, 2 H) 4.24–4.15 (m, 2 H) 2.58 (ddt, *J* = 14.0, 7.8, 1.1 Hz, 1 H) 2.54 (ddt, *J* = 14.0, 6.8, 1.3 Hz, 1 H) 2.30–2.22 (m, 1 H) 2.22–2.13 (m, 2 H) 1.73–1.64 (m, 2 H) 1.64–1.57 (m, 1 H) 1.29 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.63, 147.98, 132.24, 120.19, 119.58, 118.26 (q, J_{CF} = 319 Hz), 61.70, 50.05, 39.34, 31.99, 24.36, 18.54, 13.95; IR (film) 3080, 2940, 2868, 1733, 1676, 1641, 1431 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{13}H_{17}O_5F_3S$ 343.0822; found 343.0829.



2-acetyl-2-allyl-3,4-dihydronaphthalen-1(2H)-one (3-S7) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium carbonate (15 mmol, 2.1 g, 1.5 equiv). 2-Acetyl-1-tetralone (10 mmol, 1.88 g, 1 equiv) was dissolved in DMF (15 mL, 0.7M) and added to the flask. The reaction was stirred at rt for 10 minutes. Allyl bromide (15 mmol, 1.3 mL, 1.5 equiv) was added to the flask. The reaction was stirred at 80 °C overnight (15 h). The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (20 mL). The mixture was stirred briefly then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using

98:2 hexanes: ethyl acetate as the eluent. This procedure afforded 1.87 g (82%) of the title compound as a colorless oil.

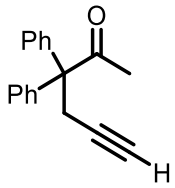
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.9, 1.5 Hz, 1 H) 7.48 (td, *J* = 7.5, 1.5 Hz, 1 H) 7.31 (t, *J* = 7.6 Hz, 1 H) 7.21 (d, *J* = 7.7 Hz, 1 H) 5.79–5.63 (m, 1 H) 5.19–5.05 (m, 2 H) 3.08 (ddd, *J* = 16.2, 10.7, 4.8 Hz, 1 H) 2.89 (dt, *J* = 17.5, 4.8 Hz, 1 H) 2.73–2.63 (m, 2 H) 2.57 (dt, *J* = 13.8, 4.7 Hz, 1 H) 2.13 (s, 3 H) 2.03 (ddd, *J* = 13.8, 10.6, 5.0 Hz, 1 H).



1-(2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)vinyl trifluoromethanesulfonate (3-5j) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with diisopropyl amine (6.15 mmol, 0.87 mL, 1.2 equiv) dissolved in THF (6 mL, 1 M). The flask was cooled to 0 °C and nBuLi (5.64 mmol, 2.5 M in hex, 2.25 mL, 1.1 equiv) was added dropwise. The reaction was stirred for 20 minutes at 0 °C then cooled to -78 °C. **2-acetyl-2-allyl-3,4-dihydronaphthalen-1(2H)-one (3-S7)** (5.12 mmol, 1.17 g, 1 equiv) dissolved in THF (5 mL, 1 M) was added dropwise added to the flask. The reaction was stirred for 20 min at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (5.64 mmol, 2.02 g, 1.1 equiv) was dissolved in THF (5 mL, 1 M) and added dropwise to the flask and the reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to rt and allowed to stir over night (15 h). The mixture was quenched with aqueous ammonium chloride (15 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a

yellow oil. The crude material was purified via column chromatography on silica gel using 98.5:1: 0.5 hexanes:ethyl acetate:triethyl amine as the eluent. This procedure afforded 1.59 g (86%) of the title compound as a light yellow oil.

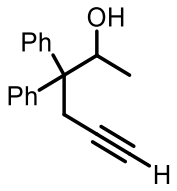
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.9, 1.4 Hz, 1 H) 7.50 (td, *J* = 7.5, 1.4 Hz, 1 H) 7.33 (t, *J* = 7.6 Hz, 1 H) 7.24 (d, *J* = 7.7 Hz, 1 H) 5.77 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1 H) 5.28 (d, *J* = 4.9 Hz, 1 H) 5.20–5.10 (m, 2 H) 4.89 (d, *J* = 4.9 Hz, 1 H) 3.09 (ddd, *J* = 17.1, 10.7, 4.5 Hz, 1 H) 2.95 (dt, *J* = 17.3, 4.7 Hz, 1 H) 2.80 (dd, *J* = 14.1, 6.9 Hz, 1 H) 2.53 (dd, *J* = 14.2, 7.6 Hz, 1 H) 2.28 (dt, *J* = 14.1, 4.7 Hz, 1 H) 2.20 (ddd, *J* = 14.5, 10.7, 4.5 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.33, 154.90, 143.17, 133.95, 132.53, 131.41, 128.81, 128.36, 127.00, 119.18, 118.28 (q, J_{CF} = 320 Hz), 105.41, 54.63, 38.84, 29.82, 25.39; IR (film) 3075, 2935, 2844, 1965, 1686, 1651, 1601, 1416 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{16}H_{15}O_4F_3S$ 361.0716; found 361.0724.



3,3-diphenylhex-5-yn-2-one (3-S8) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with sodium hydride (95%, 14 mmol, 0.336 g, 1.1 equiv). 1,1 diphenyl acetone (12.7 mmol, 2.673 g, 1.0 equiv) was dissolved in DMF (15 mL, 0.85 M) and added to the flask. The reaction was stirred at rt for 10 min until the bubbles stopped. Propargyl bromide (80% wt in toluene, 15.2 mmol, 2.26 g, 1.2 equiv) was added to the flask and the reaction heated to 80 °C with stirring overnight (15 h). The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (15 mL). The mixture was stirred briefly then transferred to a separatory funnel.

The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 2.5491 g (81%) of the title compound as a yellow-white semisolid.

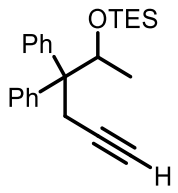
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.27 (m, 10 H) 3.20 (d, *J* = 2.7 Hz, 2 H) 2.12 (s, 3 H) 1.87 (t, *J* = 2.6 Hz, 1 H).



3,3-diphenylhex-5-yn-2-ol (3-S9) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **3,3-diphenylhex-5-yn-2-one** (**3-S8**) (17 mmol, 4.215 g, 1 equiv) and dissolved in methanol (85 mL, 0.2 M). The solution was stirred rapidly. Sodium borohydride (17.34 mmol, 656 mg, 1.02 equiv) was added in portions over 30 seconds at rt. The reaction was stirred at rt for 7 min. The reaction mixture was slowly quenched with aqueous ammonium chloride (50 mL). The mixture was stirred briefly then methanol was removed under vacuum. The solution was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil which later crystallized to a white-yellow solid. The crude material was judged to be obtained in sufficient purity to continue without

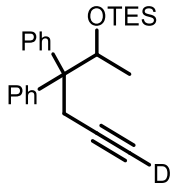
further purification. This procedure afforded 4.2514 g (>99%) of the title compound as a yellow-white semisolid.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.35–7.21 (m, 10 H) 4.83 (q, 1 H) 3.15–2.96 (m, 2 H) 1.88 (t, *J* = 2.7 Hz, 1 H) 1.10 (d, *J* = 6.3 Hz, 3 H).



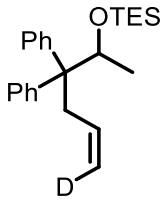
((3,3-diphenylhex-5-yn-2-yl)oxy)triethylsilane (3-S10) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with imidazole (51 mmol, 3.50 g, 3 equiv) and 4-Dimethylaminopyridine (51 mmol, 6.23 g, 3 equiv). **3,3-diphenylhex-5-yn-2-ol** (**3-S9**) (17 mmol, 4.25 g, 1.0 equiv) was dissolved in DMF (40 mL, 0.42 M) and added to the flask. Chlorotriethylsilane (51 mmol, 8.6 mL, 3 equiv) was added slowly to the flask and the reaction, then the flask was heated to 80 °C with stirring overnight (15 h). The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (50 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 5.306 g (86%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 10 H) 4.80 (q, *J* = 6.1 Hz, 1 H) 3.20 (dd, *J* = 16.4, 2.6 Hz, 1 H) 2.90 (dd, *J* = 16.4, 2.6 Hz, 1 H) 1.04 (d, *J* = 6.1 Hz, 3 H) 0.89 (t, *J* = 7.9 Hz, 9 H) 0.56 (q, *J* = 7.9 Hz, 6 H).



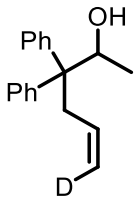
((3,3-diphenylhex-5-yn-2-yl-6-d)oxy)triethylsilane (3-S11) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **((3,3-diphenylhex-5-yn-2-yl)oxy)triethylsilane** (**3-S10**) (14.55 mmol, 5.306 g, 1 equiv) dissolved in THF and then cooled to 0 °C. nBuLi (16 mmol, 2.5 M in hex, 6.4 mL, 1.1 equiv) was added dropwise to the reaction. The reaction was stirred for 20 minutes at 0 °C. The reaction was quenched with D_2O (1.11 mmol, 20 mL, 76 equiv) and stirred for 10 minutes. The mixture was then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 5.31 g (>99%) of the title compound as a yellow oil with ~98% deuterium incorporation.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10 H) 4.82 (q, *J* = 6.1 Hz, 1 H) 3.21 (d, *J* = 16.4 Hz, 1 H) 2.92 (d, *J* = 16.3 Hz, 1 H) 1.06 (d, *J* = 6.1 Hz, 3 H) 0.91 (t, *J* = 8.0 Hz, 9 H) 0.58 (q, *J* = 7.9 Hz, 6 H).



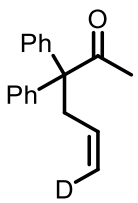
(Z)-((3,3-diphenylhex-5-en-2-yl-6-d)oxy)triethylsilane (3-S12) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with bis(cyclopentadienyl)zirconium(iv) dichloride (20.37 mmol, 5.95 g, 1.4 equiv). **((3,3-diphenylhex-5-yn-2-yl-6-d)oxy)triethylsilane** (**3-S11**) (14.55 mmol, 5.31 g, 1 equiv) was dissolved in THF (20 mL, 0.7 M) and added to the flask. The reaction was stirred for 10 minutes. Lithium tri tert-butoxy aluminum hydride (20.37 mmol, 5.18 g, 1.4 equiv) was dissolved in THF (20 mL, 1 M) and was added to the reaction. The reaction was stirred for 12 minutes at rt. The reaction was quenched with saturated ammonium chloride (20 mL) and stirred for 10 minutes. THF was removed under reduced pressure and the mixture was then transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 4.963 g (93%) of the title compound as a yellow oil (over reduced by ~1-2% as judged by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.14 (m, 10 H) 5.50–5.41 (m, 1 H) 4.87 (d, *J* = 10.3 Hz, 1 H) 4.69 (q, *J* = 6.1 Hz, 1 H) 3.01 (ddd, *J* = 14.1, 6.6, 1.3 Hz, 1 H) 2.83 (ddd, *J* = 14.1, 7.4, 1.1 Hz, 1 H) 1.02 (d, *J* = 6.2 Hz, 3 H) 0.90 (t, *J* = 7.9 Hz, 9 H) 0.57 (q, *J* = 7.7 Hz, 6 H).



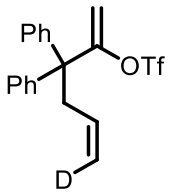
(Z)-3,3-diphenylhex-5-en-6-d-2-ol (3-S13) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **(Z)-((3,3-diphenylhex-5-en-2-yl-6-d)oxy)triethylsilane** (**3-S12**) (13.5 mmol, 4.96 g, 1 equiv) dissolved in THF (14 mL, 1 M). Tetra-n-butylammonium fluoride (40.6 mmol, 41 mL, 1 M in THF, 3 equiv) was added to the reaction. The reaction was stirred for 1 h. The reaction was quenched with saturated ammonium chloride (30 mL) and stirred for 5 minutes. The mixture was then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. The isolated product was resubjected to the reaction conditions. After work up and subsequent isolation by another column chromatography, the product was obtained in >95% purity. This procedure afforded 2.7132 g (79%) of the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.23 (m, 10 H) 5.44 (tdd, *J* = 9.5, 6.7, 2.6 Hz, 1 H) 4.97 (d, *J* = 10.1 Hz, 1 H) 4.67 (dq, *J* = 7.6, 6.3 Hz, 1 H) 3.03 (dd, *J* = 14.0, 6.7 Hz, 1 H) 2.91 (dd, *J* = 14.0, 7.4 Hz, 1 H) 1.40 (d, *J* = 8.2 Hz, 1 H) 1.09 (d, *J* = 6.2 Hz, 3 H).



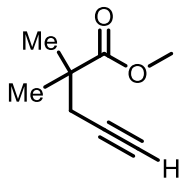
(Z)-3,3-diphenylhex-5-en-2-one-6-d (3-S14) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with oxalyl chloride (14.85 mmol, 1.3 mL, 1.1 equiv) dissolved in DCM (30 mL, 0.5 M). The reaction flask was cooled to -78 °C. Dimethyl sulfoxide (30 mmol, 2.2 mL, 2.2 equiv) was added dropwise to the flask. The reaction was stirred for 1 h at -78 °C. **(Z)-3,3-diphenylhex-5-en-6-d-2-ol** (**3-S13**) (13.5 mmol, 2.71 g, 1 equiv) dissolved in DCM (27 mL, 0.5 M) was added to the reaction while at -78 °C. The reaction was stirred for 2 hours at -78 °C. Triethyl amine (67.5 mmol, 9.5 mL) was added to the reaction and allowed to stir for an additional 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (30 mL) and stirred for 5 minutes. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 2.282 g (85%) of the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.31 (m, 4 H) 7.31–7.22 (m, 6 H) 5.53 (tdd, *J* = 9.7, 4.8, 2.4 Hz, 1 H) 4.87 (dd, *J* = 10.2, 1.1 Hz, 1 H) 3.09 (dd, *J* = 7.0, 1.2 Hz, 2 H) 2.06 (s, 3 H).



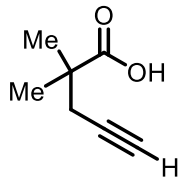
(Z)-3,3-diphenylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate (3-13) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (10.9 mmol, 2.174 g, 1.2 equiv) dissolved in THF (11 mL, 1 M). The reaction flask was cooled to -78 °C. **(Z)-3,3-diphenylhex-5-en-2-one-6-d** (**3-S14**) (9.1 mmol, 2.28, 1 equiv) was dissolved in THF (10 mL 0.9 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (10 mmol, 3.58 g, 1.1 equiv) was dissolved in THF (10 mL, 1 M) and added to the reaction while at -78 °C. The reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (20 mL) and stirred briefly. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 98.5:1:0.5 hexanes:ethyl acetate:triethyl amine as the eluent. This procedure afforded 2.8336 g (81%) of the title compound as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4 H) 7.31–7.26 (m, 6 H) 5.58 (tdd, *J* = 9.2, 4.8, 2.4 Hz, 1 H) 5.43 (d, *J* = 4.6 Hz, 1 H) 5.19 (d, *J* = 4.6 Hz, 1 H) 5.00 (dd, *J* = 10.4, 1.5 Hz, 1 H) 3.18 (dd, *J* = 6.7, 1.4 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.82, 141.36, 133.64, 129.04, 128.12, 127.26, 118.23 (t, J_{CD} = 24 Hz), 118.09 (q, J_{CF} = 320 Hz), 104.41, 56.96, 42.88; IR (film) 3057, 3027, 2922, 1955, 1650, 1599, 1495, 1418 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{16}O_3F_3SD$ 384.0986; found 384.0972.



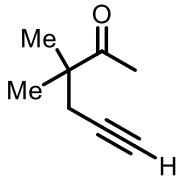
Methyl 2,2-dimethylpent-4-ynoate (3-S15) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with diisopropyl amine (30 mmol, 4.3 mL, 1.2 equiv) dissolved in THF (30 mL, 1 M). The flask was cooled to 0 °C and nBuLi (27.5 mmol, 2.5 M in hex, 11 mL, 1.1 equiv) was added dropwise. The reaction was stirred for 20 minutes at 0 °C then cooled to -78 °C. Methyl isobutyrate (25 mmol, 2.9 mL, 1.0 equiv) dissolved in THF (25 mL, 1 M) was added dropwise added to the flask. The reaction was stirred for 20 min at -78 °C. Propargyl bromide (80% wt in toluene, 30 mmol, 4.46 g, 1.2 equiv) was added dropwise to the flask and the reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to rt and allowed to stir overnight (15 h). The mixture was quenched with aqueous ammonium chloride (50 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified distillation (150 °C). This procedure afforded 2.81 g (81%) of the title compound as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 3.70 (s, 3 H) 2.44 (dd, *J* = 2.8, 1.2 Hz, 2 H) 2.00 (td, *J* = 2.7, 1.2 Hz, 1 H) 1.28 (s, 6 H).



2,2-dimethylpent-4-ynoic acid (3-S16) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with potassium hydroxide (109 mmol, 6.11 g, 5 equiv) and sodium hydroxide (24 mmol, 0.96 g, 1.1 equiv). Water (40mL) was added to the flask. **Methyl 2,2-dimethylpent-4-ynoate** (**3-S15**) (21.8 mmol, 3.0565 g, 1 equiv) was dissolved in methanol (80 mL, 0.25 M) and added to the flask. The flask was equipped with a reflux condenser and the reaction was refluxed at 80 °C for 2 hours. The reaction was cooled to rt. Methanol was removed under vacuum and then the mixture was transferred to a separatory funnel. The solution was washed with DCM (3 x 20 mL). 1 M HCl was added to the solution until the aqueous layer turned acidic (pH < 3). The acidic aqueous layer was extracted with DCM (3 x 20 mL). The combined, extracted organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 2.295 g (83%) of the title compound as a colorless oil.

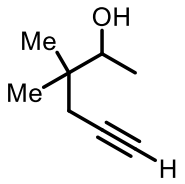
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.94 (bs, 1 H) 2.47 (d, *J* = 2.7 Hz, 2 H) 2.03 (t, *J* = 2.7 Hz, 1 H) 1.32 (s, 3 H).



3,3-dimethylhex-5-yn-2-one (3-S17) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **2,2-dimethylpent-4-ynoic acid** (**3-S16**) (18.2 mmol, 2.2949 g, 1 equiv) dissolved in diethyl ether (60 mL, 0.3 M). The flask was cooled to -78 °C and methyl lithium (58.2 mmol, 1.6 M in Et_2O, 36 mL, 3.2 equiv) was

added dropwise to the flask. The reaction was stirred for 10 minutes at -78 °C then allowed to warm to room temperature. The flask was equipped with a reflux condenser and the reaction was refluxed at 45 °C while stirring rapidly for 3 hours. The reaction was cooled to rt and quenched with saturated ammonium chloride (50 mL). The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined, extracted organic layers were washed with brine, dried over $MgSO_4$, filtered and carefully concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:diethyl ether as the eluent. Due to the volatility of the title compound, significant solvent remained after column and no accurate yield was obtained.

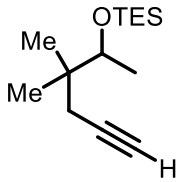
^1H NMR (700 MHz, $CDCl_3$) δ 2.40—2.37 (m, 2 H) 2.19 (s, 3 H) 2.01 (td, *J* = 2.7, 1.1 Hz, 1 H) 1.24 (s, 6 H).



3,3-dimethylhex-5-yn-2-ol (3-S18) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **3,3-dimethylhex-5-yn-2-one** (**3-S17**) (18.2 mmol, 2.260 g, 1 equiv) dissolved in methanol (50 mL, 0.33 M). The reaction was stirred rapidly and sodium borohydride (20 mmol, 757 mg, 1.1 equiv) was added in portions over 30 seconds at rt. The reaction was stirred at rt for 7 min. The reaction mixture was slowly quenched with aqueous ammonium chloride (30 mL). The mixture was stirred briefly then methanol was removed under vacuum. The solution was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20

mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a colorless oil. The crude material was purified via column chromatography on silica gel using 85:15 hexanes:ethyl acetate as the eluent. This procedure afforded 1.00 g (44% over two steps) of the title compound as a colorless oil.

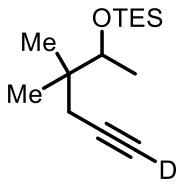
^1H NMR (700 MHz, $CDCl_3$) δ 3.72 (p, *J* = 6.2 Hz, 1 H) 2.26 (dd, *J* = 16.7, 2.7 Hz, 1 H) 2.13 (ddd, *J* = 16.7, 2.7, 0.9 Hz, 1 H) 2.01 (td, *J* = 2.7, 1.0 Hz, 1 H) 1.56 (d, *J* = 5.2 Hz, 1 H) 1.15 (dd, *J* = 6.5, 1.0 Hz, 3 H) 0.97 (s, 3 H) 0.96 (s, 3 H).



((3,3-dimethylhex-5-yn-2-yl)oxy)triethylsilane (3-S19) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with imidazole (23.8 mmol, 1.62 g, 3 equiv) and 4-Dimethylaminopyridine (23.8 mmol, 2.91 g, 3 equiv). **3,3-dimethylhex-5-yn-2-ol** (**3-S18**) (7.92 mmol, 1.00 g, 1.0 equiv) was dissolved in DMF (40 mL, 0.2 M) and added to the flask. Chlorotriethylsilane (23.8 mmol, 4 mL, 3 equiv) was added slowly to the flask and the reaction was heated to 80 °C with stirring overnight (15 h) The reaction was cooled to rt, and the mixture was quenched with aqueous ammonium chloride (30 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with water (3 x 30 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2

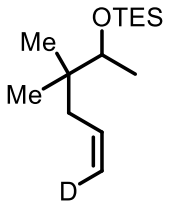
hexanes:ethyl acetate as the eluent. This procedure afforded 1.28 g (67%) of the title compound as a yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 3.68 (q, *J* = 6.3 Hz, 1 H) 2.20 (dd, *J* = 16.5, 2.7 Hz, 1 H) 2.11 (dd, *J* = 16.5, 2.7 Hz, 1 H) 1.95 (t, *J* = 2.7 Hz, 1 H) 1.07 (d, *J* = 6.3 Hz, 3 H) 0.96 (t, *J* = 7.9 Hz, 9 H) 0.925 (s, 3 H) 0.915 (s, 3 H) 0.59 (q, *J* = 7.7 Hz, 6 H).



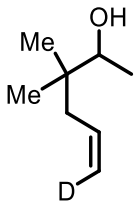
((3,3-dimethylhex-5-yn-2-yl-6-d)oxy)triethylsilane (3-S20) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **((3,3-dimethylhex-5-yn-2-yl)oxy)triethylsilane** (**3-S19**) (5.33 mmol, 1.28 g, 1 equiv) dissolved in THF. The flask was cooled to 0 °C. nBuLi (3.2 mL, 2.5 M) was added dropwise to the reaction. The reaction was stirred for 20 minutes at 0 °C. The reaction was quenched with D_2O (0.4 mmol, 7.5 mL, 75 equiv) and stirred for 10 minutes. The mixture was then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 1.28 g (>99%) of the title compound as a yellow oil (~98% deuterium incorporation).

^{1}H NMR (401 MHz, $CDCl_3$) δ 3.68 (q, *J* = 6.3 Hz, 1 H) 2.20 (d, *J* = 16.5 Hz, 1 H) 2.10 (d, *J* = 16.5 Hz, 1 H) 1.07 (d, *J* = 6.3 Hz, 3 H) 0.96 (t, *J* = 7.9 Hz, 9 H) 0.923 (s, 3 H) 0.918 (s, 3 H) 0.59 (q, *J* = 7.7 Hz, 6 H).

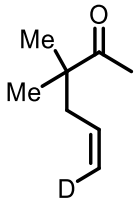


(Z)-((3,3-dimethylhex-5-en-2-yl-6-d)oxy)triethylsilane (3-S21) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with bis(cyclopentadienyl)zirconium(iv) dichloride (7.5 mmol, 2.18 g, 1.4 equiv). **((3,3-dimethylhex-5-yn-2-yl-6-d)oxy)triethylsilane** (**3-S20**) (5.33 mmol, 1.28 g, 1 equiv) was dissolved in THF (7.5 mL, 0.7 M) and added to the flask. The reaction was stirred for 10 minutes. Lithium tri tert-butoxy aluminum hydride (7.5 mmol, 1.9 g, 1.4 equiv) dissolved in THF (7.5 mL, 1 M) and was added to the reaction. The reaction was stirred for 12 minutes at rt. The reaction was quenched with saturated ammonium chloride (10 mL) and stirred for 10 minutes. THF was removed under reduced pressure and then the mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 1.20g (93%) of the title compound as a yellow oil (over reduced by ~1% as judged by ^{1}HNMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (dtt, *J* = 10.0, 7.4, 2.5 Hz, 1 H) 4.99 (d, *J* = 10.1 Hz, 1 H) 3.56–3.44 (m, 1 H) 2.03 (dd, *J* = 13.4, 7.2 Hz, 1 H) 1.96 (dd, *J* = 13.5, 7.7 Hz, 1 H) 1.06 (d, *J* = 6.3 Hz, 3 H) 0.96 (t, *J* = 7.9 Hz, 9 H) 0.82 (s, 3 H) 0.79 (s, 3 H) 0.58 (q, *J* = 7.6 Hz, 6 H).

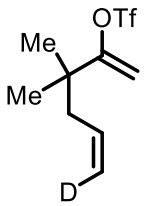


(Z)-3,3-dimethylhex-5-en-6-d-2-ol (3-S22) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **(Z)-((3,3-dimethylhex-5-en-2-yl-6-d)oxy)triethylsilane** (**3-S21**) (4.93 mmol, 1.20 g, 1 equiv) dissolved in THF (5 mL, 1 M). Tetra-n-butylammonium fluoride (15 mmol, 1 M in THF, 15 mL, 3 equiv) was added to the flask. The reaction was stirred for 1 h. The reaction was quenched with saturated ammonium chloride (10 mL) and stirred for 5 minutes. The mixture was then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. The isolated product was resubjected to the reaction conditions. After work up and subsequent isolation by another column chromatography, the product was obtained in >95% purity. This procedure afforded 0.417 g (66%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.90–5.83 (m, 1 H) 5.03 (d, *J* = 10.1 Hz, 1 H) 3.54 (p, *J* = 6.0 Hz, 1 H) 2.10 (dd, *J* = 13.6, 7.6 Hz, 1 H) 1.99 (dd, *J* = 13.6, 7.4 Hz, 1 H) 1.39 (d, *J* = 5.1 Hz, 1 H) 1.13 (d, *J* = 6.4 Hz, 3 H) 0.88 (s, 3 H) 0.86 (s, 3 H).



(Z)-3,3-dimethylhex-5-en-2-one-6-d (3-S23) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with oxalyl chloride (3.6 mmol, 310 µL, 1.1 equiv) dissolved in DCM (1 mL, 0.33 M). The reaction flask was cooled to -78 °C. Dimethyl sulfoxide (7.1 mmol, 500 µL, 2.2 equiv) was added dropwise to the flask. The reaction was stirred for 1 h at -78 °C. **(Z)-3,3-dimethylhex-5-en-6-d-2-ol** (**3-S22**) (3.22 mmol, 0.414 g, 1 equiv) dissolved in DCM (6 mL, 0.5 M) was added to the reaction while at -78 °C. The reaction was stirred for 2 hours at -78 °C. Triethyl amine (16.1 mmol, 2.24 mL) was added to the reaction and allowed to stir for an additional 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir overnight (15 h). The reaction was quenched with saturated ammonium chloride (10 mL) and stirred for 5 minutes. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:diethyl ether as the eluent. Due to the volatility of the title compound, significant solvent remained after column and no accurate yield was obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (dtq, *J* = 9.8, 4.9, 2.4 Hz, 1 H) 5.03 (d, *J* = 10.1 Hz, 1 H) 2.26 (d, *J* = 7.4 Hz, 2 H) 2.12 (s, 3 H) 1.12 (s, 6 H).



(Z)-3,3-dimethylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate (3-16) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and

charged with potassium hexamethyldisilazane (3.86 mmol, 770 mg, 1.2 equiv) dissolved in THF (4 mL, 1 M). The reaction flask was cooled to -78 °C. **(Z)-3,3-dimethylhex-5-en-2-one-6-d (3-S23)** (3.2 mmol, 0.40 g, 1 equiv) was dissolved in THF (4 mL, 0.7 M) and added dropwise to the flask. The reaction was stirred for 20 minutes at -78 °C. N-(2-pyridyl)bis(trifluoromethanesulfonimide) (3.54 mmol, 1.27 g, 1.1 equiv) was dissolved in THF (3.5 mL, 1 M) and added to the reaction while at -78 °C. The reaction was stirred for 30 minutes at -78 °C. The reaction was warmed to 0 °C and allowed to stir for 3 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and stirred briefly. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 99: 1 hexanes: DCM as the eluent. This procedure afforded 20 mg (2%) of the title compound as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 5.70 (dtt, *J* = 9.9, 7.4, 2.5 Hz, 1 H) 5.13 (d, *J* = 4.3 Hz, 1 H) 5.09 (d, *J* = 10.1 Hz, 1 H) 4.92 (d, *J* = 4.4 Hz, 1 H) 2.19 (d, *J* = 7.3 Hz, 2 H) 1.15 (s, 6 H).

Preparation and Characterization of Products

General Procedure for Pd-catalyzed Alkene Dialkylation Reactions on terminal alkenes, General Procedure A (butane)

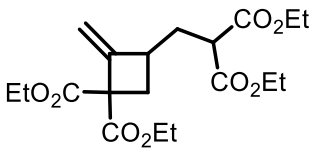
A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with Pd(OAc)2 (0.008 mmol, 0.04 equiv), Tris(2,4-di-tert-butylphenyl)phosphite (0.012 mmol, 0.06 equiv), and lithium tert-butoxide (1.00

mmol, 5 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. The alkenyl triflate (0.2 mmol, 1.0 equiv) was weighed in a dram vial and diluted with 1,4 dioxane (1 mL, 0.2M). This mixture was added to the Schlenk tube and diethyl malonate (1 mmol, 5 equiv) was added. 1,4 dioxane (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 60 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General Procedure for Pd-catalyzed Alkene Dialkylation Reactions on terminal alkenes, General Procedure B (pentane)

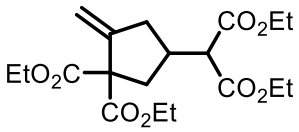
A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with Pd(OAc)2 (0.008 mmol, 0.04 equiv), 1,2-Bis(diphenylphosphino)benzene (0.012 mmol, 0.06 equiv), and lithium tert-butoxide (1.00 mmol, 5 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. The alkenyl triflate (0.2 mmol, 1.0 equiv) was weighed in a dram vial and diluted with 1,4 dioxane (1 mL, 0.2M). This mixture was added to the Schlenk tube and diethyl malonate (1 mmol, 5 equiv) was added. 1,4 dioxane (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 95 °C with stirring for 1 hour until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The

aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel to afford the desired product.



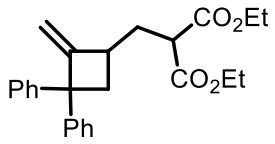
Diethyl 3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-methylenecyclobutane-1,1-dicarboxylate (3-6aa) The title compound was prepared from **3-5a** (0.2 mmol, 75.1 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 65.6 mg (85%) of the title compound as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38–3.35 (m, 1 H) 5.18–5.10 (m, 1 H) 4.26–4.13 (m, 8 H) 3.36 (t, *J* = 7.6 Hz, 1 H) 3.06–2.97 (m, 1 H) 2.67 (dd, *J* = 11.9, 9.3 Hz, 1 H) 2.30–2.20 (m, 2 H) 2.04 (ddd, *J* = 14.0, 9.2, 7.7 Hz, 1 H) 1.30–1.21 (m, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.35, 169.15, 168.98, 168.87, 147.32, 110.70, 61.75, 61.60, 61.53, 61.51, 59.12, 49.72, 38.22, 32.82, 31.79, 14.04, 13.99; IR (film) 2980, 2939, 1726, 1673, 1449 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{28}O_8$ 385.1857; found 385.1866.



Diethyl 4-(1,3-diethoxy-1,3-dioxopropan-2-yl)-2-methylenecyclopentane-1,1-dicarboxylate (3-7aa) The title compound was prepared from **3-5a** (0.2 mmol, 75.0 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 59.6 mg (77%) of the title compound as a colorless oil.

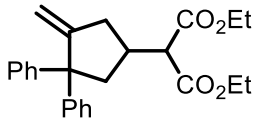
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37–5.31 (m, 1 H) 5.29–5.23 (m, 1 H) 4.27–4.13 (m, 8 H) 3.24 (d, *J* = 9.0 Hz, 1 H) 2.78–2.61 (m, 3 H) 2.24 (ddt, *J* = 18.2, 12.5, 2.8 Hz, 1 H) 2.21–2.03 (m, 1 H) 1.30–1.19 (m, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.16, 170.09, 168.29, 168.23, 145.95, 112.93, 63.10, 61.71, 61.68, 61.42, 56.30, 39.79, 38.37, 36.80, 14.07, 13.98, 13.94; IR (film) 2979, 2934, 1727, 1654, 1448 cm^{-1}; HRMS (ESI^+ TOF) m/z: [M + H^+]$^+$ calcd for $C_{19}H_{28}O_8$ 385.1857; found 385.1864.



Diethyl 2-((2-methylene-3,3-diphenylcyclobutyl)methyl)malonate (3-6b) The title compound was prepared from **3-5b** (0.2 mmol, 77.1 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 58.2 mg (74%) of the title compound as a yellow oil.

Diethyl 2-((2-methylene-3,3-diphenylcyclobutyl)methyl)malonate (3-6b) The title compound was prepared from **3-5b** (21.6 mmol, 8.2474 g) and diethyl malonate (108 mmol, 16.5 mL), $Pd(OAc)_2$ (0.864 mmol, 0.19 g), Tris(2,4-di-tert-butylphenyl)phosphite (0.864 mmol, 0.559 g), lithium tert-butoxide (108 mmol, 8.645 g) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 6.358 g (75%) of the title compound as a yellow oil.

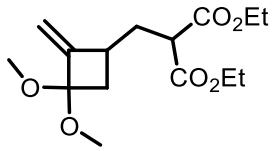
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.12 (m, 10 H) 5.22–5.16 (m, 1 H) 5.07–5.02 (m, 1 H) 4.20 (dqd, *J* = 10.9, 7.1, 2.0 Hz, 4 H) 3.39 (t, *J* = 7.5 Hz, 1 H) 2.95 (ttd, *J* = 11.0, 5.3, 4.9, 2.5 Hz, 1 H) 2.77 (dd, *J* = 10.6, 8.8 Hz, 1 H) 2.53 (dd, *J* = 10.6, 8.6 Hz, 1 H) 2.37 (ddd, *J* = 13.5, 8.0, 5.2 Hz, 1 H) 2.08 (ddd, *J* = 13.9, 9.6, 7.1 Hz, 1 H) 1.28 (t, *J* = 7.1 Hz, 3 H) 1.25 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.41, 169.16, 158.34, 146.28, 146.18, 128.23, 128.09, 127.58, 127.24, 126.14, 125.91, 106.74, 61.45, 61.41, 58.40, 50.00, 38.76, 38.06, 32.29, 14.06, 14.01; IR (film) 3056, 2980, 2932, 1739, 1728, 1667, 1601, 1492 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: [M + H$^+$]$^+$ calcd for $C_{25}H_{28}O_4$ 393.2060; found 393.2062.



Diethyl 2-(4-methylene-3,3-diphenylcyclopentyl)malonate (3-7b) The title compound was prepared from **3-5b** (0.2 mmol, 76.4 mg) and diethyl malonate (0.4 mmol, 64μL), sodium tert-butoxide (0.4 mmol, 38.4 mg) and toluene (0.1M) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 55.6 mg (71%) of the title compound (4:1 ratio of regiomers) as a yellow oil. The reported peaks are for the mixture of 4:1 regiomers.

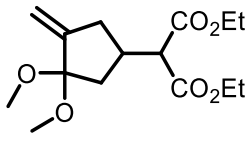
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 4 H) 7.26–7.18 (m, 3 H) 7.18–7.13 (m, 1.5 H) 7.09–7.03 (m, 1.5 H) 5.23–5.18 (m, 0.75 H) 5.18–5.14 (m, 0.22 H) 5.04–5.01 (m, 0.22 H) 4.63–4.58 (m, 0.75 H) 4.25–4.10 (m, 4 H) 3.37 (t, *J* = 7.5 Hz, 0.23 H) 3.28 (d, *J* = 9.8 Hz, 0.77 H) 2.98–2.86 (m, 0.35 H) 2.86–2.72 (m, 1.75 H) 2.64–2.54 (m, 0.82 H) 2.51 (dd, *J* =

10.6, 8.6 Hz, 0.23 H) 2.40–2.33 (m, 1 H) 2.32–2.25 (m, 0.75 H) 2.06 (ddd, *J* = 14.0, 9.6, 7.1 Hz, 0.23 H) 1.32–1.20 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.61, 168.57, 155.88, 146.83, 145.10, 128.38, 128.25, 128.23, 128.19, 128.08, 127.81, 127.57, 127.24, 126.28, 126.14, 125.94, 125.90, 111.38, 106.73, 61.44, 61.40, 61.32, 61.28, 60.57, 57.12, 49.99, 46.10, 38.75, 38.05, 37.22, 35.32, 32.28, 14.09, 14.05, 14.00; IR (film) 3057, 2980, 2932, 1747, 1729, 1596, 1490, 1443 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: [M + NH_4^+]$^+$ calcd for $C_{25}H_{28}O_4$ 410.2326; found 410.2329.



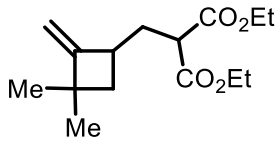
Diethyl 2-((3,3-dimethoxy-2-methylenecyclobutyl)methyl)malonate (3-6c) The title compound was prepared from **3-5c** (0.4 mmol, 115.9 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 86.0 mg (72%) of the title compound as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25–5.16 (m, 1 H) 5.09–5.03 (m, 1 H) 4.19 (q, *J* = 7.0 Hz, 4 H) 3.35 (t, *J* = 7.6 Hz, 1 H) 3.21 (s, 6 H) 2.73–2.63 (m, 1 H) 2.35–2.23 (m, 2 H) 2.05–1.95 (m, 1 H) 1.79 (dd, *J* = 11.4, 7.1 Hz, 1 H) 1.26 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.27, 169.10, 151.48, 107.67, 102.14, 61.42, 50.22, 49.61, 49.01, 37.50, 34.05, 32.89, 14.04; IR (film) 2982, 2938, 2827, 1747, 1730, 1441 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: [M + Na^+]$^+$ calcd for $C_{15}H_{24}O_6$ 323.1465; found 323.1469.



Diethyl 2-(3,3-dimethoxy-4-methylenecyclopentyl)malonate (3-7c) The title compound was prepared **3-5c** (0.2 mmol, 58.3 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 99:1 hexanes:ethyl acetate -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 50.7 mg (84%) of the title compound as a colorless oil.

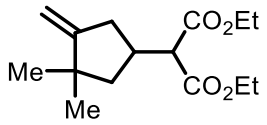
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17–5.12 (m, 1 H) 5.11–5.05 (m, 1 H) 4.24–4.13 (m, 4 H) 3.27 (d, *J* = 10.2 Hz, 1 H) 3.22 (s, 3 H) 3.15 (s, 3 H) 2.75 (h, *J* = 8.5 Hz, 1 H) 2.64 (dd, *J* = 16.5, 8.6 Hz, 1 H) 2.23 (dd, *J* = 12.6, 7.6 Hz, 1 H) 2.15 (ddt, *J* = 16.7, 8.4, 2.6 Hz, 1 H) 1.61 (dd, *J* = 12.6, 9.3 Hz, 1 H) 1.29–1.21 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.48, 145.85, 109.72, 105.67, 61.29, 57.33, 49.99, 49.12, 40.01, 34.53, 33.21, 14.08, 14.07; IR (film) 2980, 2937, 2829, 1749, 1730, 1445 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{24}O_6$ 300.1573; found 269.1375 $[M–HOCH_3+H^+]^+$ (elimination product).



Diethyl 2-((3,3-dimethyl-2-methylenecyclobutyl)methyl)malonate (3-6d) The title compound was prepared from **3-5d** (0.2 mmol, 52.1 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 46.7 mg (86%) of the title compound (3:2 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 3:2 regiomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81–4.77 (m, 0.4 H) 4.77–4.72 (m, 1.60 H) 4.25–4.13 (m, 4 H) 3.35 (t, *J* = 7.6 Hz, 0.6 H) 3.16 (d, *J* = 9.8 Hz, 0.4 H) 2.97–2.87 (m, 0.6 H) 2.74–2.60 (m, 0.8 H) 2.26 (ddd, *J* = 13.7, 8.0, 5.7 Hz, 0.6 H) 2.19–2.10 (m, 0.4 H) 2.01–1.89 (m, 1.3

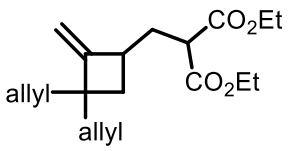
H) 1.81–1.74 (m, 0.4 H) 1.42 (dd, *J* = 10.7, 7.7 Hz, 0.6 H) 1.29–1.24 (m, 6 H) 1.15 (s, 2 H) 1.12 (s, 3 H) 1.05 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.54, 169.34, 168.78, 168.75, 162.83, 159.82, 103.75, 101.53, 61.33, 61.31, 61.25, 61.21, 57.41, 50.13, 46.53, 41.82, 41.42, 38.73, 38.18, 37.05, 35.93, 33.38, 29.74, 29.68, 28.75, 28.09, 27.69, 14.10, 14.06, 14.05; IR (film) 2956, 2861, 1742, 1733, 1671, 1462 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{24}O_4$ 269.1747; found 269.1742.



Diethyl 2-(3,3-dimethyl-4-methylenecyclopentyl)malonate (3-7d) The title compound was prepared from **3-5d** (0.2 mmol, 51.6 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 40.0 mg (75%) of the title compound as a colorless oil.

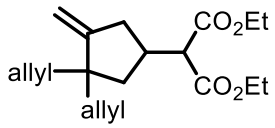
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83–4.79 (m, 1 H) 4.78–4.73 (m, 1 H) 4.25–4.16 (m, 4 H) 3.17 (d, 1 H) 2.76–2.61 (m, 2 H) 2.21 (m, 1 H) 1.82 (m, 1 H) 1.36–1.30 (m, 1 H) 1.30–1.25 (m, 6 H) 1.13 (s, 3 H) 1.06 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.77, 168.75, 159.82, 103.75, 61.25, 61.21, 57.41, 46.53, 41.82, 38.18, 35.93, 29.74, 28.75, 14.10; IR (film) 2957, 2864, 1741, 1731, 1654, 1463 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{15}H_{24}O_4$ 269.1747; found 269.1745.

1750, 1731, 1670, 1444 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_4$ 295.1904; found 295.1905.



Diethyl 2-((3,3-diallyl-2-methylenecyclobutyl)methyl)malonate (3-6e) The title compound was prepared from **3-5e** (0.2 mmol, 62.3 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 53.4 mg (83%) of the title compound (3:1 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 3:1 regiomers.

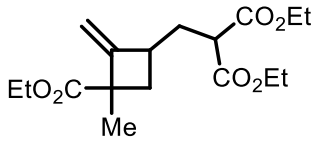
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.68 (m, 2 H) 5.09–4.99 (m, 4 H) 4.98–4.94 (m, 0.27 H) 4.89–4.84 (m, 0.8 H) 4.79–4.76 (m, 0.76 H) 4.74–4.71 (m, 0.26 H) 4.25–4.13 (m, 4 H) 3.34 (t, *J* = 7.6 Hz, 0.75 H) 3.14 (d, *J* = 9.6 Hz, 0.25 H) 2.84–2.75 (m, 0.75 H) 2.66–2.53 (m, 0.55 H) 2.27–2.08 (m, 5 H) 1.99–1.92 (m, 0.75 H) 1.92–1.86 (m, 0.80 H) 1.82 (dd, *J* = 12.7, 6.7 Hz, 0.31 H) 1.53 (dd, *J* = 11.3, 7.7 Hz, 0.84 H) 1.40–1.36 (m, 0.3 H) 1.30–1.21 (m, 7 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.48, 169.29, 159.03, 155.83, 135.21, 135.01, 134.88, 134.70, 117.49, 117.44, 117.22, 117.18, 105.86, 104.30, 61.35, 61.32, 61.25, 61.20, 57.36, 50.05, 47.90, 47.37, 44.55, 43.99, 42.56, 42.27, 40.45, 39.23, 36.68, 35.95, 33.52, 32.94, 31.49, 30.31, 14.09, 14.06, 14.04; IR (film) 3073, 2977, 2925, 1750, 1732, 1639, 1443 cm^{-1}; HRMS (ESI^{+} TOF) m/z: $[M + H^{+}]^{+}$ calcd for $C_{19}H_{28}O_4$ 321.2060; found 321.2050.



Diethyl 2-(3,3-diallyl-4-methylenecyclopentyl)malonate (3-7e) The title compound was prepared from **3-5e** (0.2 mmol, 62.3 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl

acetate as the eluent. This procedure afforded 51.1 mg (79%) of the title compound as a colorless oil.

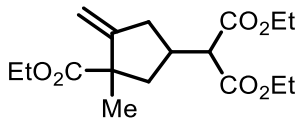
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.67 (m, 2 H) 5.08–4.99 (m, 4 H) 4.98–4.94 (m, 1 H) 4.75–4.69 (m, 1 H) 4.23–4.12 (m, 4 H) 3.14 (d, *J* = 9.5 Hz, 1 H) 2.67–2.52 (m, 2 H) 2.22–2.02 (m, 5 H) 1.82 (dd, *J* = 12.6, 6.4 Hz, 1 H) 1.39 (t, *J* = 11.9 Hz, 1 H) 1.29–1.21 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.74, 168.60, 155.83, 135.20, 135.01, 117.49, 117.44, 105.86, 61.25, 61.20, 57.35, 47.90, 44.55, 43.99, 40.45, 39.23, 35.95, 14.09; IR (film) 3070, 2976, 2903, 1750, 1731, 1636, 1436 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{28}O_4$ 321.2060; found 321.2048.



Diethyl 2-((3-(ethoxycarbonyl)-3-methyl-2-methylenecyclobutyl)methyl)malonate (3-6f) The title compound was prepared from **3-5f** (0.2 mmol, 63.6 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 56.6 mg (86%) of the title compound (3:1 ratio of regiomers and 3:1 diastereomers) as a colorless oil. The reported peaks are for the mixture of 3:1 regiomers and 3:1 diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08–5.05 (m, 0.53 H) 5.03–5.01 (m, 0.22 H) 5.01–4.99 (m, 0.13 H) 4.98–4.95 (m, 0.42 H) 4.95–4.92 (m, 0.22 H) 4.92–4.89 (m, 0.53 H) 4.25–4.08 (m, 6 H) 3.41–3.32 (m, 0.73 H) 3.27 (d, *J* = 9.7 Hz, 0.2 H) 3.20 (d, *J* = 9.8 Hz, 0.06 H) 3.05–2.90 (m, 0.73 H) 2.90–2.82 (m, 0.7 H) 2.74 (dd, *J* = 11.3, 9.3 Hz, 0.29 H) 2.69–2.59 (m, 0.43 H) 2.50 (dd, *J* = 12.9, 6.3 Hz, 0.07 H) 2.32–2.16 (m, 1.82 H) 2.06–1.98 (m, 0.76

H) 1.95 (dd, *J* = 11.5, 9.2 Hz, 0.57 H) 1.89–1.82 (m, 0.22 H) 1.50 (dd, *J* = 11.3, 7.8 Hz, 0.25 H) 1.44 (s, 1.63 H) 1.41 (s, 0.69 H) 1.36 (s, 0.26 H) 1.33 (s, 0.72 H) 1.29–1.22 (m, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.64, 174.70, 174.34, 169.34, 169.32, 169.17, 169.13, 168.62, 168.52, 155.66, 155.20, 154.43, 153.75, 108.14, 107.56, 106.21, 105.99, 61.45, 61.43, 61.39, 61.37, 61.34, 61.28, 60.84, 60.78, 60.68, 56.96, 56.81, 52.12, 51.82, 50.39, 49.92, 49.87, 49.56, 43.25, 42.35, 38.89, 38.48, 37.92, 37.02, 36.83, 36.60, 35.41, 33.74, 33.55, 32.75, 25.51, 25.08, 24.22, 23.82, 14.16, 14.09, 14.05; IR (film) 2978, 2929, 1747, 1727, 1668, 1444 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_6$ 327.1802; found 327.1803.



Diethyl 2-(3-(ethoxycarbonyl)-3-methyl-4-methylenecyclopentyl)malonate (3-7f)

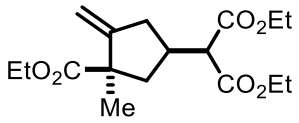
The title compound was prepared from **3-5f** (0.2 mmol, 63.6 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 47.8 mg (73%) of the title compound compound (2:1 ratio of diastereomers) as a colorless oil. The reported peaks are for the mixture of 2:1 diastereomers.

Diethyl 2-(3-(ethoxycarbonyl)-3-methyl-4-methylenecyclopentyl)malonate (3-7f)

The title compound was prepared from **3-5f** (3 mmol, 948.9 mg) and diethyl malonate (15 mmol, 2.3 mL), $Pd(OAc)_2$ (0.12 mmol, 27 mg), Tris(2,4-di-tert-butylphenyl)phosphite (0.18 mmol, 80.4 mg), lithium tert-butoxide (15 mmol, 1.2 g) using General Procedure A. The

crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 714.7 mg (73%) of the title compound (2:1 ratio of diastereomers) as a colorless oil. The reported peaks are for the mixture of 2:1 diastereomers.

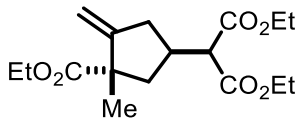
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04–4.99 (m, 0.7 H) 4.99–4.93 (m, 1.3 H) 4.25–4.16 (m, 4 H) 3.27 (d, *J* = 9.6 Hz, 0.62 H) 3.20 (d, *J* = 9.6 Hz, 0.33 H) 2.87 (dtd, *J* = 17.2, 10.4, 7.0 Hz, 0.34 H) 2.74 (ddt, *J* = 16.2, 7.7, 1.7 Hz, 0.36 H) 2.69–2.60 (m, 1.33 H) 2.51 (dd, *J* = 12.9, 6.5 Hz, 0.37 H) 2.31–2.16 (m, 1.72 H) 1.87 (ddd, *J* = 12.4, 5.9, 2.2 Hz, 0.67 H) 1.37 (s, 1 H) 1.34 (s, 2 H) 1.30–1.20 (m, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.64, 175.45, 168.62, 168.52, 168.49, 154.43, 153.75, 108.14, 107.56, 61.37, 61.34, 61.28, 60.84, 60.77, 56.96, 56.81, 52.12, 51.82, 43.25, 42.35, 38.89, 37.92, 37.02, 36.60, 25.51, 25.08, 14.09, 14.05, 14.01; IR (film) 2980, 2923, 2852, 1750, 1727, 1655, 1450 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_6$ 327.1802; found 327.1795.



Diethyl 2-((1R,3R)-3-(ethoxycarbonyl)-3-methyl-4-methylenecyclopentyl)malonate (3-S24) The mixture of diastereomers was purified via column chromatography on silica gel using 99.8:0.2 DCM:ethyl acetate as the eluent. This procedure afforded 450 mg (63%) of the title compound as a colorless oil.

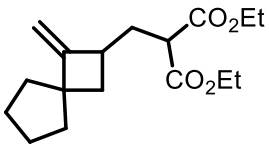
^{1}H NMR (700 MHz, $CDCl_3$) δ 4.97–4.94 (m, 2 H) 4.24–4.16 (m, 4 H) 4.16–4.08 (m, 2 H) 3.27 (d, *J* = 9.7 Hz, 1 H) 2.69–2.60 (m, 2 H) 2.29–2.22 (m, 1 H) 2.22–2.15 (m, 1 H) 1.86 (dd, *J* = 12.8, 6.3 Hz, 1 H) 1.33 (s, 3 H) 1.29–1.20 (m, 9 H); ^{13}C NMR (176 MHz, $CDCl_3$)

δ 175.65, 168.63, 168.53, 154.44, 107.57, 61.37, 61.35, 60.84, 56.80, 51.82, 42.34, 38.89, 36.60, 25.50, 14.09, 14.08, 14.04; IR (film) 2981, 2925, 2852, 1750, 1726, 1655, 1449 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_6$ 327.1802; found 327.1803.



Diethyl 2-((1R,3S)-3-(ethoxycarbonyl)-3-methyl-4-methylenecyclopentyl)malonate (3-S25) The mixture of diastereomers was purified via column chromatography on silica gel using 99.8:0.2 DCM:ethyl acetate as the eluent. This procedure afforded 215 mg (30%) of the title compound as a colorless oil.

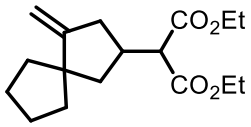
^1H NMR (700 MHz, $CDCl_3$) δ 5.02–4.97 (m, 2 H) 4.23–4.15 (m, 4 H) 4.14–4.06 (m, 2 H) 3.18 (d, *J* = 9.7 Hz, 1 H) 2.85 (dtd, *J* = 17.4, 10.3, 7.0 Hz, 1 H) 2.73 (dd, *J* = 16.2, 7.5 Hz, 1 H) 2.49 (dd, *J* = 12.9, 6.5 Hz, 1 H) 2.20 (ddt, *J* = 16.1, 10.4, 2.8 Hz, 1 H) 1.36 (s, 3 H) 1.34–1.30 (m, 1 H) 1.29–1.18 (m, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.43, 168.51, 168.48, 153.74, 108.12, 61.26, 60.75, 56.94, 52.10, 43.24, 37.90, 37.01, 25.06, 14.07, 14.00; IR (film) 2979, 2920, 2853, 1750, 1727, 1654, 1452 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_6$ 327.1802; found 327.1801.



Diethyl 2-((1-methylenespiro[3.4]octan-2-yl)methyl)malonate (3-6g) The title compound was prepared from **3-5g** (0.2 mmol, 57.0 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 50.0 mg (85%) of the title

compound (3:2 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 3:2 regiomers.

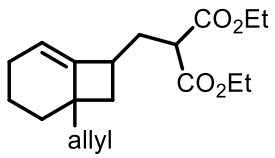
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82–4.79 (m, 0.41 H) 4.79–4.76 (m, 0.43 H) 4.76–4.70 (m, 1.15 H) 4.24–4.12 (m, 4 H) 3.36 (t, *J* = 7.6 Hz, 0.54 H) 3.18 (d, *J* = 10.0 Hz, 0.37 H) 2.89–2.80 (m, 0.59 H) 2.68 (dd, *J* = 16.0, 7.6 Hz, 0.46 H) 2.64–2.52 (m, 0.50 H) 2.24 (ddd, *J* = 13.8, 7.9, 5.9 Hz, 0.64 H) 2.15 (ddt, *J* = 15.4, 10.0, 2.4 Hz, 0.50 H) 2.05–1.99 (m, 0.68 H) 1.99–1.93 (m, 0.56 H) 1.85 (dd, 0.51 H) 1.79–1.42 (m, 9 H) 1.32 (m, 6.5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.56, 169.36, 168.78, 162.39, 159.18, 103.42, 101.29, 61.32, 61.30, 61.24, 61.19, 57.22, 53.36, 52.29, 50.13, 45.25, 41.53, 39.91, 39.66, 38.78, 38.39, 38.32, 37.73, 36.51, 33.21, 24.99, 24.67, 24.57, 24.39, 14.10, 14.06; IR (film) 2951, 2869, 1750, 1731, 1670, 1444 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{17}H_{26}O_4$ 295.1904; found 295.1905.



Diethyl 2-(4-methylenespiro[4.4]nonan-2-yl)malonate (3-7g) The title compound was prepared from **3-5g** (0.2 mmol, 56.6 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 47.8 mg (82%) of the title compound as a colorless oil.

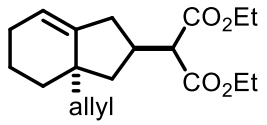
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82–4.79 (m, 1 H) 4.78–4.73 (m, 1 H) 4.24–4.12 (m, 4 H) 3.18 (d, *J* = 10.0 Hz, 1 H) 2.68 (ddt, *J* = 15.9, 7.7, 1.7 Hz, 1 H) 2.64–2.53 (m, 1 H) 2.15 (ddt, *J* = 14.5, 10.0, 2.2 Hz, 1 H) 1.85 (dd, *J* = 12.1, 6.0 Hz, 1 H) 1.79–1.65 (m, 3 H) 1.65–1.51 (m, 4 H) 1.51–1.43 (m, 1 H) 1.33–1.29 (m, 1 H) 1.29–1.19 (m, 6 H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 168.80, 159.20, 103.44, 61.25, 61.20, 57.22, 53.37, 45.26, 41.54, 39.66, 38.40, 36.51, 25.00, 24.67, 14.10; IR (film) 2943, 2868, 1751, 1733, 1650, 1447 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{17}H_{26}O_4$ 317.1723; found 317.1720.



Diethyl 2-((1-allylbicyclo[4.2.0]oct-5-en-7-yl)methyl)malonate (3-6h) The title compound was prepared from **3-5h** (0.2 mmol, 62.1 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 57.7 mg (90%) of the title compound (1:1 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 1:1 regiomers.

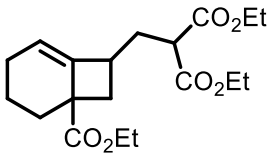
^1H NMR (500 MHz, $CDCl_3$) δ 5.85–5.70 (m, 1 H) 5.36–5.30 (m, 1 H) 5.10–5.01 (m, 2 H) 4.24–4.13 (m, 4 H) 3.30 (t, *J* = 7.5 Hz, 0.51 H) 3.16 (d, *J* = 9.8 Hz, 0.45 H) 3.13–3.06 (m, 1 H) 2.84–2.69 (m, 0.93 H) 2.36–2.21 (m, 1.66 H) 2.19–2.10 (m, 1 H) 2.09–2.02 (m, 1.5 H) 2.02–1.88 (m, 3 H) 1.74 (dt, *J* = 12.4, 3.5 Hz, 0.57 H) 1.66–1.52 (m, 2.18 H) 1.30–1.23 (m, 6 H) 1.17 (t, *J* = 9.2 Hz, 0.64 H) 1.01 (dtd, *J* = 25.5, 12.8, 4.3 Hz, 1.12 H) 0.88 (dd, *J* = 12.2, 10.2 Hz, 0.57 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.59, 169.42, 168.93, 168.77, 147.50, 145.46, 135.68, 135.00, 118.35, 117.08, 116.75, 113.23, 61.34, 61.31, 61.22, 61.17, 58.08, 50.38, 45.00, 43.82, 42.22, 41.94, 39.73, 38.96, 38.35, 34.59, 34.25, 32.69, 31.97, 24.80, 24.39, 18.72, 17.98, 14.10, 14.07, 14.05; IR (film) 2976, 2929, 2849, 1745, 1729, 1640, 1445 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{28}O_4$ 321.2060; found 321.2056.



Diethyl 2-((2S,3aS)-3a-allyl-2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)malonate (3-7h)

The title compound was prepared from **3-5h** (0.2 mmol, 61.8 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 60.0 mg (94%) of the title compound compound (93:7 ratio of diastereomers) as a colorless oil. The reported peaks are for the mixture of 93:7 diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 15.2, 11.9, 7.5 Hz, 1 H) 5.36–5.29 (m, 1 H) 5.08–5.04 (m, 1 H) 5.04–4.98 (m, 1 H) 4.24–4.11 (m, 4 H) 3.27 (d, *J* = 10.4 Hz, 0.07 H) 3.16 (d, *J* = 9.8 Hz, 0.92 H) 2.86–2.69 (m, 1.76 H) 2.34–2.19 (m, 0.26 H) 2.15–1.80 (m, 7 H) 1.69–1.57 (m, 2 H) 1.30–1.21 (m, 6 H) 0.99 (td, *J* = 12.9, 4.4 Hz, 1 H) 0.92–0.80 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.93, 168.77, 145.46, 135.00, 118.35, 117.08, 61.22, 61.17, 58.08, 43.82, 42.21, 38.96, 34.59, 34.24, 31.96, 24.80, 17.98, 14.10; IR (film) 2976, 2928, 2853, 1750, 1731, 1637, 1446 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{19}H_{28}O_4$ 343.1880; found 343.1881.

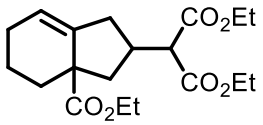


Diethyl 2-((1-(ethoxycarbonyl)bicyclo[4.2.0]oct-5-en-7-yl)methyl)malonate (3-6i)

The title compound was prepared from **3-5i** (0.2 mmol, 68.4 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 56.5 mg (80%) of the title compound

(3:1 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 3:1 regiomers.

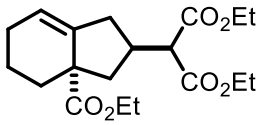
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53–5.49 (m, 0.21 H) 5.47–5.41 (m, 0.73 H) 4.25–4.09 (m, 6 H) 3.42–3.32 (m, 0.76 H) 3.30 (t, *J* = 7.5 Hz, 0.76 H) 3.17 (d, *J* = 9.9 Hz, 0.23 H) 2.91–2.81 (m, 0.27 H) 2.76–2.65 (m, 0.26 H) 2.50 (dd, *J* = 10.2, 8.5 Hz, 0.8 H) 2.43–2.35 (m, 0.49 H) 2.35–2.28 (m, 0.8 H) 2.28–2.21 (m, 0.83 H) 2.17–1.90 (m, 3.23 H) 1.76–1.66 (m, 1.07 H) 1.59–1.47 (m, 1.74 H) 1.44–1.36 (m, 0.42 H) 1.29–1.22 (m, 9 H) 1.19–1.11 (, 0.55 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.42, 169.42, 169.23, 168.59, 142.47, 140.04, 120.97, 114.85, 61.42, 61.41, 61.28, 60.71, 60.64, 57.43, 53.03, 51.94, 50.21, 43.54, 43.19, 39.57, 35.47, 35.11, 32.74, 32.71, 31.75, 24.84, 24.19, 19.87, 19.63, 14.22, 14.08, 14.04; 2979, 2933, 2857, 1748, 1724, 1446 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + NH_4^+]^+$ calcd for $C_{19}H_{28}O_6$ 370.2224; found 370.2219.



Diethyl 2-(3a-(ethoxycarbonyl)-2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)malonate (3-7i) The title compound was prepared from **3-5i** (0.5 mmol, 172 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was then removed by distillation under vacuum at 95 °C. This procedure afforded 141 mg (80%) of the title compound (4:1 ratio of diastereomers) as a yellow oil. The reported peaks are for the mixture of 4:1 diastereomers.

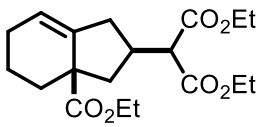
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.54–5.50 (m, 1 H) 4.23–4.09 (m, 6 H) 3.26 (d, *J* = 10.6 Hz, 0.18 H) 3.17 (d, *J* = 10.0 Hz, 0.77 H) 2.90–2.83 (m, 0.8 H) 2.75–2.67 (m, 0.79 H) 2.63–

2.55 (m, 0.19 H) 2.46 (dd, *J* = 13.9, 7.2 Hz, 0.19 H) 2.42–2.30 (m, 2.03 H) 2.11–2.03 (m, 1.84 H) 2.02–1.90 (m, 1.52 H) 1.73–1.66 (m, 1.02 H) 1.53–1.46 (m, 0.19 H) 1.45–1.37 (m, 0.87 H) 1.28–1.22 (m, 9.82 H) 1.16 (ddd, *J* = 14.0, 12.7, 3.1 Hz, 1.12 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 176.59, 175.79, 168.70, 168.67, 168.59, 168.58, 140.82, 140.04, 120.97, 120.46, 61.28, 61.27, 60.70, 60.65, 57.56, 57.43, 53.03, 50.48, 43.19, 41.81, 38.37, 36.13, 35.47, 35.11, 32.89, 32.70, 24.84, 24.36, 19.77, 19.63, 14.21, 14.16, 14.08; IR (film) 2979, 2934, 2862, 1749, 1721, 1445; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{19}H_{28}O_6$ 353.1959; found 353.1958.



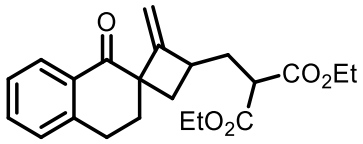
Diethyl 2-((2R,3aS)-3a-(ethoxycarbonyl)-2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)malonate (3-S26) The mixture of diastereomers was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 110 mg (78%) of the title compound as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56–5.51 (m, 1 H) 4.23–4.07 (m, 6 H) 3.17 (d, *J* = 9.9 Hz, 1 H) 2.92–2.81 (m, 1 H) 2.78–2.64 (m, 1 H) 2.44–2.32 (m, 2 H) 2.13–1.92 (m, 3 H) 1.75–1.64 (m, 1 H) 1.48–1.36 (m, 1 H) 1.30–1.20 (m, 10 H) 1.16 (td, *J* = 13.4, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.80, 168.58, 140.04, 120.97, 61.29, 61.27, 60.71, 57.43, 53.03, 43.19, 35.47, 35.11, 32.71, 24.84, 19.63, 14.21, 14.08; IR (film) 2979, 2933, 2866, 1750, 1725, 1446 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + NH_4^+]^+$ calcd for $C_{19}H_{28}O_6$ 370.2224; found 370.2218.



Diethyl 2-((2R,3aR)-3a-(ethoxycarbonyl)-2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)malonate (3-S27) The mixture of diastereomers was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 25 mg (18%) of the title compound as a colorless oil.

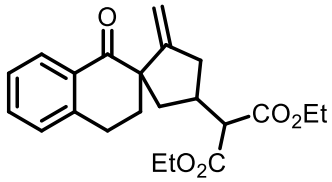
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56–5.50 (m, 1 H) 4.24–4.07 (m, 6 H) 3.26 (d, *J* = 10.6 Hz, 1 H) 2.59 (qt, *J* = 10.1, 7.4 Hz, 1 H) 2.46 (dd, *J* = 13.9, 7.2 Hz, 1 H) 2.40—2.29 (m, 2 H) 2.11–1.89 (m, 4 H) 1.73–1.65 (m, 1 H) 1.54–1.45 (m, 1 H) 1.30–1.22 (m, 9 H) 1.18 (td, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.59, 168.70, 168.68, 140.82, 120.46, 61.28, 60.65, 57.57, 50.48, 41.81, 38.37, 36.13, 32.90, 24.35, 19.77, 14.16, 14.08; IR (film) 2979, 2933, 2868, 1740, 1725, 1445 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{19}H_{28}O_6$ 375.1778; found 375.1777.



Diethyl 2-((2-methylene-1'-oxo-3',4'-dihydro-1'H-spiro[cyclobutane-1,2'-naphthalen]-3-yl)methyl)malonate (3-6j) The title compound was prepared from **3-5j** (0.2 mmol, 72.4 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 62.5 mg (84%) of the title compound (3:1 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 3:1 regiomers. Regiomers can be partially separated via column chromatography on silica gel using 20:2:78 DCM:ethyl acetate:hexanes as the eluent (see spectra).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–7.99 (m, 1 H) 7.51–7.42 (m, 1 H) 7.35–7.28 (m, 1 H) 7.25–7.20 (m, 1 H) 4.99–4.94 (m, 0.33 H) 4.93–4.90 (m, 0.62 H) 4.62–4.60 (m, 0.6 H)

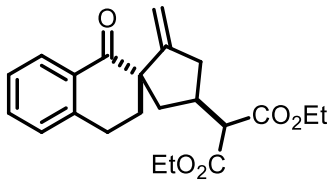
4.60–4.55 (m, 0.32 H) 4.26–4.13 (m, 4 H) 3.44–3.38 (m, 0.64 H) 3.32 (d, *J* = 9.9 Hz, 0.27 H) 3.22 (ddd, *J* = 16.7, 11.2, 5.1 Hz, 0.66 H) 3.15–3.07 (m, 0.37 H) 3.07–2.99 (m, 0.66 H) 2.96–2.86 (m, 1 H) 2.83–2.72 (m, 0.64 H) 2.60 (dd, *J* = 11.2, 7.9 Hz, 0.64 H) 2.41–2.16 (m, 3 H) 2.10–2.00 (m, 1 H) 2.00–1.94 (m, 0.32 H) 1.85 (dd, *J* = 11.1, 9.3 Hz, 0.64 H) 1.31–1.22 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.59, 196.45, 169.35, 169.23, 168.74, 168.68, 153.84, 152.47, 143.84, 143.78, 133.34, 133.30, 132.42, 131.99, 128.78, 128.77, 128.16, 128.07, 126.69, 108.33, 106.78, 61.43, 61.41, 61.38, 61.37, 56.87, 56.40, 55.16, 49.78, 40.38, 38.90, 36.69, 36.22, 33.46, 33.11, 32.38, 29.83, 26.14, 25.58, 14.11, 14.09, 14.07; IR (film) 2979, 2933, 2850, 1747, 1729, 1681, 1600, 1453 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{26}O_5$ 371.1853; found 371.1855.



Diethyl 2-(2-methylene-1'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-4-yl)malonate (3-7j) The title compound was prepared from **3-5j** (0.2 mmol, 71.5 mg) using General Procedure B except the reaction was stirred for 15 hours. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 62.8 mg (85%) of the title compound (3:1 ratio of diastereomers) as a yellow oil. The reported peaks are for the mixture of 3:1 diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08–8.02 (m, 1 H) 7.50–7.43 (m, 1 H) 7.34–7.28 (m, 1 H) 7.25–7.20 (m, 1 H) 5.09–5.04 (m, 0.64 H) 4.99–4.95 (m, 0.34 H) 4.78–4.73 (m, 0.65 H) 4.60–4.56 (m, 0.33 H) 4.25–4.11 (m, 4 H) 3.33 (d, *J* = 9.9 Hz, 0.33 H) 3.24 (d, *J* = 9.2 Hz,

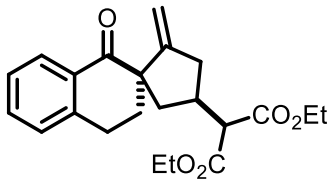
0.63 H) 3.15–3.07 (m, 0.38 H) 3.05–3.00 (m, 1.27 H) 2.99–2.73 (m, 2.43 H) 2.52–2.44 (m, 0.66 H) 2.40–2.29 (m, 1.69 H) 2.29–2.23 (m, 0.39 H) 2.23–2.15 (m, 0.38 H) 2.09–1.94 (m, 1.42 H) 1.61–1.52 (m, 0.59 H) 1.31–1.20 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.65, 199.59, 168.74, 168.68, 168.47, 168.43, 153.21, 152.47, 143.84, 143.43, 133.34, 133.21, 132.42, 131.46, 128.77, 128.61, 128.29, 128.16, 126.73, 126.69, 108.33, 107.99, 61.41, 61.37, 61.32, 61.28, 56.87, 56.72, 56.51, 56.40, 40.98, 40.38, 38.98, 38.90, 36.22, 36.03, 35.00, 33.46, 26.49, 25.58, 14.11, 14.09, 14.04; IR (film) 2980, 2924, 2851, 1750, 1730, 1677, 1601, 1450 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{26}O_5$ 371.1853; found 371.1851.



Diethyl 2-((1S,4R)-2-methylene-1'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-4-yl)malonate (3-S28) The mixture of diastereomers was purified via column chromatography on silica gel using 99.8:0.2 DCM:ethyl acetate as the eluent. This procedure afforded 45 mg (72%) of the title compound as a colorless oil.

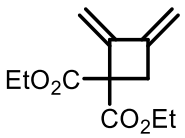
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 1.4 Hz, 1 H) 7.46 (td, *J* = 7.4, 1.4 Hz, 1 H) 7.30 (t, *J* = 7.6 Hz, 1 H) 7.22 (d, *J* = 7.6 Hz, 1 H) 5.09–5.04 (m, 1 H) 4.78–4.72 (m, 1 H) 4.24–4.10 (m, 4 H) 3.24 (d, *J* = 9.0 Hz, 1 H) 3.08–2.97 (m, 2 H) 2.90–2.77 (m, 2 H) 2.48 (dd, *J* = 12.1, 6.9 Hz, 1 H) 2.39–2.28 (m, 2 H) 2.02 (dt, *J* = 13.4, 5.1 Hz, 1 H) 1.55 (dd, *J* = 12.8, 10.7 Hz, 1 H) 1.28–1.20 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.61, 168.44, 168.40, 153.19, 143.41, 133.19, 131.44, 128.59, 128.27, 126.71, 107.97, 61.30, 61.26, 56.71, 56.50, 40.98, 38.98, 36.02, 35.00, 26.48, 14.09, 14.04; IR (film) 2980, 2926, 2852,

1749, 1730, 1680, 1601, 1453 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{26}O_5$ 371.1853; found 371.1850.



Diethyl 2-((1R,4R)-2-methylene-1'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-4-yl)malonate (3-S29) The mixture of diastereomers was purified via column chromatography on silica gel using 99.8:0.2 DCM:ethyl acetate as the eluent. This procedure afforded 14 mg (22%) of the title compound as a colorless oil.

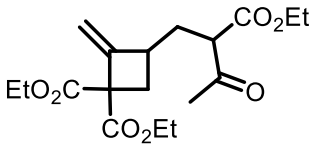
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1 H) 7.47 (t, *J* = 7.4 Hz, 1 H) 7.31 (t, *J* = 7.5 Hz, 1 H) 7.24 (d, *J* = 7.6 Hz, 1 H) 4.99–4.94 (m, 1 H) 4.62–4.56 (m, 1 H) 4.25–4.13 (m, 4 H) 3.33 (d, *J* = 9.8 Hz, 1 H) 3.11 (ddd, *J* = 17.2, 9.2, 4.8 Hz, 1 H) 2.92 (dt, *J* = 17.3, 5.4 Hz, 1 H) 2.84–2.72 (m, 2 H) 2.41–2.30 (m, 1 H) 2.30–2.23 (m, 1 H) 2.22–2.15 (m, 1 H) 2.05 (ddd, *J* = 13.7, 9.1, 4.6 Hz, 1 H) 1.97 (dd, *J* = 12.8, 5.9 Hz, 1 H) 1.31–1.24 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.56, 168.71, 168.65, 152.46, 143.82, 133.32, 132.40, 128.75, 128.14, 126.67, 108.31, 61.39, 61.35, 56.86, 56.40, 40.37, 38.89, 36.22, 33.45, 25.57, 14.10, 14.08; IR (film) 2972, 2924, 2849, 1748, 1730, 1680, 1600, 1454 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{22}H_{26}O_5$ 371.1853; found 371.1854.



Diethyl 2,3-dimethylenecyclobutane-1,1-dicarboxylate (3-11a) The title compound was prepared from **3-5a** (0.2 mmol, 74.9 mg) using General Procedure A excluding the diethyl malonate. The crude material was purified via column chromatography on silica

gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 10 mg (22%) of the title compound as a colorless oil.

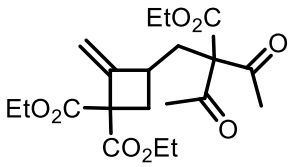
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45–5.41 (m, 1 H) 5.31–5.28 (m, 1 H) 5.27–5.24 (m, 1 H) 4.90–4.86 (m, 1 H) 4.28–4.16 (m, 4 H) 3.24–3.17 (m, 2 H) 1.27 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.02, 145.37, 143.15, 107.91, 106.22, 61.74, 58.35, 36.93, 14.01; IR (film) 3452, 2980, 2921, 2849, 1728, 1450 cm^{-1}; HRMS (ESI^+ TOF) m/z: [M + H^+]$^+$ calcd for $C_{12}H_{16}O_4$ 225.1779; found 449.2152 [M_2+H^+]$^+$ and 471.1977 [M_2+Na^+]$^+$.



Diethyl 3-(2-(ethoxycarbonyl)-3-oxobutyl)-2-methylenecyclobutane-1,1-dicarboxylate (3-6ab) The title compound was prepared from **3-5a** (0.2 mmol, 75.3 mg) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 37.5 mg (53%) of the title compound (88:12 ratio of regiomers) as a colorless oil. The reported peaks are for the mixture of 88:12 regiomers and enol tautomer.

^{1}H NMR (401 MHz, $CDCl_3$) δ 12.89 (s, 0.13 H) 5.37–5.32 (m, 0.77 H) 5.32—5.30 (m, 0.05 H) 5.30–5.27 (m, 0.14 H) 5.27–5.22 (m, 0.09 H) 5.15–5.08 (m, 0.76 H) 5.07–5.03 (m, 0.16 H) 4.28–4.11 (m, 6 H) 3.50–3.39 (m, 0.80 H) 3.34–3.28 (m, 0.09 H) 3.17–3.05 (m, 0.16 H) 3.03–2.88 (m, 0.77 H) 2.64 (ddd, *J* = 12.1, 9.4, 2.9 Hz, 1 H) 2.48 (dd, *J* = 14.5, 7.1 Hz, 0.19 H) 2.43–2.35 (m, 0.21 H) 2.31 (dd, *J* = 12.1, 7.1 Hz, 0.21 H) 2.26–2.11 (m, 4 H) 2.05–1.87 (m, 1.34 H) 1.30–1.21 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.49, 202.32, 173.41, 173.14, 169.47, 169.31, 169.28, 169.25, 168.88, 168.83, 148.23, 147.39, 147.32,

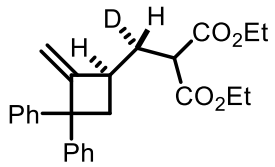
110.79, 110.60, 110.44, 97.81, 64.39, 61.74, 61.60, 61.55, 61.53, 60.40, 59.10, 59.04, 58.92, 57.45, 57.12, 40.21, 39.72, 39.61, 38.24, 38.18, 36.52, 36.42, 32.03, 31.97, 31.75, 31.67, 31.62, 30.47, 29.65, 28.83, 28.80, 19.25, 14.22, 14.03, 14.01, 13.98, 13.96, 13.92. IR (film) 2967, 2958, 2931, 2871, 1716, 1463, 1445 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{18}H_{26}O_7$ 355.1751; found 355.1739 $[M+H^+]^+$.



Diethyl 3-(2-acetyl-2-(ethoxycarbonyl)-3-oxobutyl)-2-methylenecyclobutane-1,1-dicarboxylate (3-S30) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with dry magnesium chloride (1.06 mmol, 101 mg, 2 equiv) dissolved in acetonitrile (2 mL, 0.5 M). The flask was cooled to 0 °C. Triethyl amine was added to the flask (1.06 mmol, 150 µL, 2 eq). **3-6ab** (0.53 mmol, 189 mg, 1 equiv) was added to the flask dissolved in acetonitrile (2 mL, 0.25 M). The reaction was stirred for 20 minutes. Acyl chloride (0.53 mmol, 38 µL, 1 equiv) was added to the flask. The reaction was stirred for an additional hour at 0 °C then allowed to warm to rt and stir for 15 h. The reaction was quenched with HCl (5 mL, 1 M). The mixture was then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 90:10 hexanes:ethyl acetate as the eluent. This procedure afforded 94.5 mg (45%) of the title compound (88:12 ratio of regiomers) as a colorless oil. The reported peaks are for the major regiomer only.

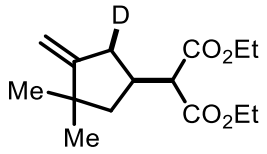
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37–5.34 (m, 0.88 H) 5.19–5.15 (m, 0.79 H) 4.32–4.12 (m, 6 H) 3.04–2.94 (m, 1 H) 2.59 (dd, *J* = 12.0, 9.1 Hz, 1 H) 2.52 (dd, *J* = 14.5, 2.7 Hz, 1 H) 2.33–2.15 (m, 8 H) 1.32–1.20 (m, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 201.30, 201.18, 169.21, 168.82, 168.26, 147.81, 109.94, 62.22, 61.71, 61.56, 59.46, 37.02, 36.60, 34.17, 28.59, 28.40, 14.04, 13.96, 13.88. IR (film) 2981, 2933, 2905, 1726, 1725, 1445 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{20}H_{28}O_8$ 419.1676; found 419.1662 $[M+Na^+]^+$.

Preparation and Characterization of Deuterium Labeled Products



Diethyl 2-((2-methylene-3,3-diphenylcyclobutyl)methyl-d)malonate (3-14) The title compound was prepared from **(Z)-3,3-diphenylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate** (**3-13**) (7.39 mmol, 2.817 g) and diethyl malonate (37 mmol, 5.6 mL), $Pd(OAc)_2$ (0.30 mmol, 66 mg), Tris(2,4-di-tert-butylphenyl)phosphite (0.44 mmol, 0.287 g), lithium tert-butoxide (37 mmol, 3.00 g) using General Procedure A. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Excess diethyl malonate was removed by distillation under vacuum at 95 °C. This procedure afforded 1.7969 g (62%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.14 (m, 10 H) 5.20–5.15 (m, 1 H) 5.07–5.00 (m, 1 H) 4.24–4.13 (m, 4 H) 3.37 (d, *J* = 8.0 Hz, 1 H) 2.98–2.88 (m, 1 H) 2.76 (dd, *J* = 10.5, 8.9 Hz, 1 H) 2.51 (dd, *J* = 10.6, 8.6 Hz, 1 H) 2.33 (dd, *J* = 8.0, 5.2 Hz, 1 H) 1.31–1.19 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.43, 169.18, 158.35, 146.30, 146.19, 128.24, 128.21, 128.10, 127.58, 127.25, 126.15, 125.92, 106.75, 61.45, 61.42, 58.40, 49.93,

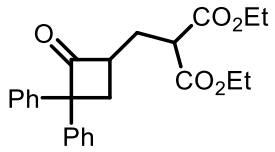
38.71, 37.98, 31.94 (t, J_{CD} = 19.7 Hz), 14.05, 14.01; IR (film) 3056, 2981, 2937, 2180–1885, 1749, 1731, 1669, 1598, 1491, 1445; HRMS (ESI$^+$ TOF) m/z: [M + Na$^+$]$^+$ calcd for $C_{25}H_{27}DO_4$ 416.1943; found 416.1937.



Diethyl 2-((1S,5S)-3,3-dimethyl-4-methylenecyclopentyl-5-d)malonate (3-17) The title compound was prepared from **(Z)-3,3-dimethylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate (3-16)** (0.08 mmol, 20 mg), diethyl malonate (0.16 mmol, 24 µL), $Pd(OAc)_2$ (0.003 mmol, 0.7 mg), 1,2-Bis(diphenylphosphino)benzene (0.0047 mmol, 2.1 mg), lithium tert-butoxide (0.16 mmol, 13 mg) using General Procedure B. The crude material was purified via column chromatography on silica gel using 98:2 hexanes:ethyl acetate as the eluent. This procedure afforded 16.2 mg (75%) of the title compound as a colorless oil.

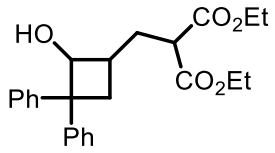
^{1}H NMR (700 MHz, $CDCl_3$) δ 4.81–4.78 (m, 1 H) 4.77–4.72 (m, 1 H) 4.20 (q, *J* = 7.1 Hz, 4 H) 3.16 (d, *J* = 9.5 Hz, 1 H) 2.71–2.62 (m, 2 H) 1.78 (ddd, *J* = 12.3, 5.6, 2.5 Hz, 1 H) 1.30–1.28 (m, 1 H) 1.28–1.24 (m, 6 H) 1.12 (s, 3 H) 1.05 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.81, 168.78, 159.79, 103.79, 61.26, 61.22, 57.37, 46.53, 41.83, 37.78 (t, J_{CD} = 19.4 Hz), 35.83, 29.74, 28.72, 14.10; IR (film) 2970, 2957, 2932, 2865, 1741, 1732, 1653, 1463 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: [M + Na$^+$]$^+$ calcd for $C_{15}H_{23}DO_4$ 292.1630; found 292.1622.

Preparation and Characterization of Cyclized Product



Diethyl 2-((2-oxo-3,3-diphenylcyclobutyl)methyl)malonate (3-S31) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-methylene-3,3-diphenylcyclobutyl)methyl)malonate (3-6b)** (16.2 mmol, 6.39 g, 1 equiv) dissolved in DCM (150 mL, 0.11 M). The reaction flask was cooled to -78 °C. Ozone was bubbled through the reaction until the solution turned a dark blue color. Nitrogen gas was then bubbled through the solution to remove excess ozone. An excess of dimethyl sulfide was added to the flask and the reaction was stirred at -78 °C for an additional hour. The reaction was warmed to rt and stirred overnight (15 h). The solvents were removed under vacuum without additional work up. The crude material was purified via column chromatography on silica gel using 49:49:1 hexanes:DCM:ethyl acetate as the eluent. This procedure afforded 1.28 g (20%) of the title compound as a yellow oil.

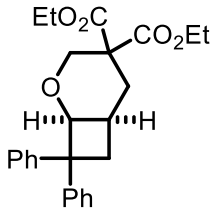
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.14 (m, 10 H) 4.26–4.09 (m, 4 H) 3.55 (dd, *J* = 8.2, 6.8 Hz, 1 H) 3.50–3.39 (m, 1 H) 3.10 (t, *J* = 10.9 Hz, 1 H) 2.48 (dd, *J* = 11.2, 8.7 Hz, 1 H) 2.35 (dt, *J* = 14.0, 6.9 Hz, 1 H) 2.14 (dt, *J* = 14.0, 8.3 Hz, 1 H) 1.31–1.19 (m, 6 H).



Diethyl 2-((2-hydroxy-3,3-diphenylcyclobutyl)methyl)malonate (3-S32) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-oxo-3,3-diphenylcyclobutyl)methyl)malonate (3-S31)**

(3.24 mmol, 1.278 g, 1 equiv) dissolved in methanol (30 mL, 0.1 M). The reaction was stirred rapidly and sodium borohydride (3.5 mmol, 131mg, 1.05 equiv) was added in portions over 30 seconds at rt. The reaction was stirred at rt for 7 min. The reaction mixture was slowly quenched with aqueous ammonium chloride (30 mL). The mixture was stirred briefly then methanol was removed under vacuum. The solution was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a colorless oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 1.23 g (96%) of the title compound as a colorless oil. The reported peaks are for an unassigned mixture of 3:2 diastereomers.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.42–7.10 (m, 10 H) 4.99 (td, *J* = 5.5, 3.4 Hz, 0.37 H) 4.38 (dd, *J* = 11.4, 7.4 Hz, 0.63 H) 4.25–4.09 (m, 4 H) 3.48–3.33 (m, 1 H) 3.03 (dd, *J* = 11.7, 7.6 Hz, 0.62 H) 2.79 (dd, *J* = 11.2, 9.0 Hz, 0.42 H) 2.64 (ddd, *J* = 11.3, 8.0, 3.3 Hz, 0.43 H) 2.44 (ddd, *J* = 13.3, 8.9, 6.7 Hz, 0.45 H) 2.25–2.04 (m, 2.58 H) 1.93 (dt, *J* = 13.8, 6.8 Hz, 0.45 H) 1.64 (dd, *J* = 11.7, 9.7 Hz, 0.70 H) 1.58–1.54 (m, 0.74 H) 1.31–1.18 (m, 6 H).

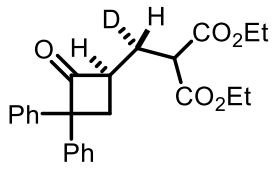


Diethyl 8,8-diphenyl-2-oxabicyclo[4.2.0]octane-4,4-dicarboxylate (3-S33) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-hydroxy-3,3-diphenylcyclobutyl)methyl)malonate (3-S32)** (3.1 mmol, 1.23 g, 1 equiv) dissolved in DMF (4 mL, 0.75 M). Diiodomethane (3.63 mmol,

300 µL, 1.1 equiv) was added to the flask. Sodium hydride (95%, 7.26 mmol, 175 mg, 2.2 equiv) was added to the flask. The reaction was stirred at 80 °C overnight (15 h). The reaction mixture was quenched with aqueous ammonium chloride (5 mL). The solution was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (3 x 15 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a colorless oil. The crude material was purified via column chromatography on silica gel using 95: 5 hexanes:ethyl acetate as the eluent. Further purification was required, and the title compound was further purified via column chromatography on silica gel using 35:64:1 DCM:hexanes:ethyl acetate as the eluent. This procedure afforded 94 mg (7%) of the title compound as a colorless oil.

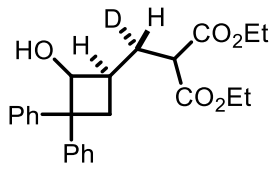
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 2 H) 7.33 (t, *J* = 7.8 Hz, 2 H) 7.27–7.17 (m, 5 H) 7.15–7.10 (m, 1 H) 6.20–6.15 (m, 1 H) 5.98 (dd, *J* = 6.3, 3.5 Hz, 1 H) 5.56–5.51 (m, 1 H) 4.19 (q, *J* = 7.1 Hz, 2 H) 4.12–4.01 (m, 2 H) 2.93 (dd, *J* = 10.8, 9.4 Hz, 1 H) 2.90–2.84 (m, 1 H) 2.72 (ddd, *J* = 11.1, 7.7, 3.5 Hz, 1 H) 2.61 (ddd, *J* = 14.8, 6.8, 1.2 Hz, 1 H) 2.47 (dd, *J* = 14.8, 8.2 Hz, 1 H) 1.28 (t, *J* = 7.1 Hz, 3 H) 1.17 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.91, 154.82, 146.45, 143.13, 138.44, 128.60, 128.00, 127.46, 126.73, 126.22, 126.01, 125.58, 80.88, 63.98, 60.67, 54.35, 36.61, 33.27, 31.18, 14.19, 14.18; IR (film) 2980, 2925, 2850, 1739, 1716, 1626, 1598, 1494, 1450 cm^{-1}; HRMS (ESI^+ TOF) m/z: $[M + H^+]^+$ calcd for $C_{25}H_{28}O_5$ 426.2275; found 426.2268.

Preparation and Characterization of Cyclized Deuterium-Labeled Product



Diethyl 2-((2-oxo-3,3-diphenylcyclobutyl)methyl-d)malonate (3-S34) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-methylene-3,3-diphenylcyclobutyl)methyl-d)malonate** (**3-14**) (4.57 mmol, 1.796 g, 1 equiv) dissolved in DCM (45 mL, 0.1 M). The reaction flask was cooled to -78 °C. Ozone was bubbled through the reaction until the solution turned a dark blue color. Nitrogen gas was then bubbled through the solution to remove excess ozone. An excess of dimethyl sulfide was added to the flask and the reaction was stirred at -78 °C for an additional hour. The reaction was warmed to rt and stirred overnight (15 h). The solvents were removed under vacuum without additional work up. The crude material was purified via column chromatography on silica gel using 49:49:1 hexanes:DCM:ethyl acetate as the eluent. This procedure afforded 0.367 g (20%) of the title compound as a yellow oil.

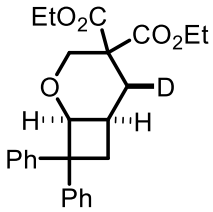
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 8 H) 7.25–7.15 (m, 2 H) 4.25–4.12 (m, 4 H) 3.54 (d, *J* = 6.7 Hz, 1 H) 3.48–3.41 (m, 1 H) 3.15–3.05 (m, 1 H) 2.48 (dd, *J* = 11.3, 8.8 Hz, 1 H) 2.33 (t, *J* = 7.0 Hz, 1 H) 1.30–1.22 (m, 6 H).



Diethyl 2-((2-hydroxy-3,3-diphenylcyclobutyl)methyl-d)malonate (3-S35) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-oxo-3,3-diphenylcyclobutyl)methyl-d)malonate (3-S34)**

(0.93 mmol, 0.367 g, 1 equiv) dissolved in methanol (10 mL, 0.1 M). The reaction was stirred rapidly and sodium borohydride (0.974 mmol, 37mg, 1.05 equiv) was added in portions over 30 seconds at rt. The reaction was stirred at rt for 7 min. The reaction mixture was slowly quenched with aqueous ammonium chloride (10 mL). The mixture was stirred briefly then methanol was removed under vacuum. The solution was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a colorless oil. The crude material was judged to be obtained in sufficient purity to continue without further purification. This procedure afforded 0.356 g (97%) of the title compound as a colorless oil. The reported peaks are for an unassigned mixture of 3:2 diastereomers.

NMR (500 MHz, $CDCl_3$) δ 7.42–7.07 (m, 10 H) 4.99 (td, *J* = 5.5, 3.3 Hz, 0.35 H) 4.38 (dd, *J* = 11.3, 8.2 Hz, 0.56 H) 4.26–4.12 (m, 4 H) 3.42 (d, *J* = 7.0 Hz, 0.50 H) 3.37 (d, *J* = 7.6 Hz, 0.36 H) 3.03 (dd, *J* = 11.6, 8.4 Hz, 0.58 H) 2.79 (dd, *J* = 11.2, 8.9 Hz, 0.41 H) 2.64 (ddd, *J* = 11.3, 8.1, 3.3 Hz, 0.40 H) 2.43 (qd, *J* = 8.5, 5.9 Hz, 0.38 H) 2.21–2.06 (m, 1.84 H) 1.64 (dd, *J* = 11.7, 10.3 Hz, 0.62 H) 1.59–1.55 (m, 0.76 H) 1.29–1.18 (m, 6 H).

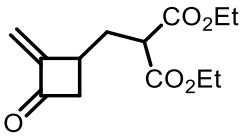


Diethyl (1S,5S,6R)-8,8-diphenyl-2-oxabicyclo[4.2.0]octane-4,4-dicarboxylate-5-d (3-15) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **diethyl 2-((2-hydroxy-3,3-diphenylcyclobutyl)methyl-d)malonate (3-S35)** (0.87 mmol, 0.35 g, 1 equiv) dissolved in DMF (1.5 mL, 0.5 M).

Diiodomethane (0.96 mmol, 78 µL, 1.1 equiv) was added to the flask. Sodium hydride (95%, 1.92 mmol, 46 mg, 2.2 equiv) was added to the flask. The reaction was stirred at 80 °C overnight (15 h). The reaction mixture was quenched with aqueous ammonium chloride (5 mL). The solution was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (3 x 10 mL), brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. Further purification was required and the title compound was purified via column chromatography on silica gel using 35:64:1 DCM:hexanes:ethyl acetate as the eluent. This procedure afforded 34 mg (10%) of the title compound as a colorless oil.

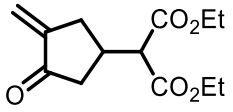
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 2 H) 7.32 (t, *J* = 7.6 Hz, 2 H) 7.25–7.21 (m, 2 H) 7.22–7.17 (m, 3 H) 7.12 (t, *J* = 7.0 Hz, 1 H) 6.17–6.14 (m, 1 H) 5.96 (dd, *J* = 6.5, 3.5 Hz, 1 H) 5.53 (m, 1 H) 4.18 (q, *J* = 7.1 Hz, 2 H) 4.10–4.00 (m, 2 H) 2.95–2.88 (m, 1 H) 2.88–2.81 (m, 1 H) 2.70 (ddd, *J* = 11.2, 7.7, 3.5 Hz, 1 H) 2.57 (d, *J* = 6.8 Hz, 1 H) 1.28 (t, *J* = 7.0 Hz, 3 H) 1.16 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.91, 154.81, 146.44, 143.10, 138.38, 128.58, 127.98, 127.45, 126.72, 126.19, 125.99, 125.61, 80.88, 63.97, 60.66, 54.33, 36.53, 33.18, 30.82 (t, J_{CD} = 19.4 Hz), 14.18, 14.17; IR (film) 2980, 2924, 2850, 1740, 1714, 1627, 1597, 1494, 1447 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + H^+]^+$ calcd for $C_{25}H_{27}DO_5$ 427.2338; found 427.2328.

Deprotection of Acetal Products



Diethyl 2-((2-methylene-3-oxocyclobutyl)methyl)malonate (3-S36) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with pyridinium p-toluenesulfonate (0.17 mmol, 42.7 mg, 1 equiv). **Diethyl 2-((3,3-dimethoxy-2-methylenecyclobutyl)methyl)malonate (3-6c)** (0.17 mmol, 50 mg, 1 equiv) was dissolved in THF (1 mL, 0.1 M) and water (1 mL, 0.1 M) and added to the flask. The reaction was heated to 50 °C and stirred overnight (15 h). The reaction was cooled to rt then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 20 mg (47%) of the title compound as a light yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.76 (dd, *J* = 2.8, 1.1 Hz, 1 H) 5.16 (dd, *J* = 2.4, 1.1 Hz, 1 H) 4.24–4.15 (m, 4 H) 3.40 (t, *J* = 7.6 Hz, 1 H) 3.12 (dd, *J* = 17.5, 9.0 Hz, 1 H) 2.98 (dqt, *J* = 8.8, 6.2, 3.1 Hz, 1 H) 2.62 (dd, *J* = 17.5, 5.9 Hz, 1 H) 2.31 (ddd, *J* = 14.0, 7.5, 6.6 Hz, 1 H) 2.15 (ddd, *J* = 14.0, 9.1, 7.7 Hz, 1 H) 1.29–1.20 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.83, 168.96, 168.80, 157.70, 113.02, 61.65, 50.56, 50.53, 33.37, 33.10, 14.04; IR (film) 2981, 2921, 2849, 1735, 1726, 1654, 1450, 1444; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{13}H_{18}O_5$ 277.1046; found 277.1041.



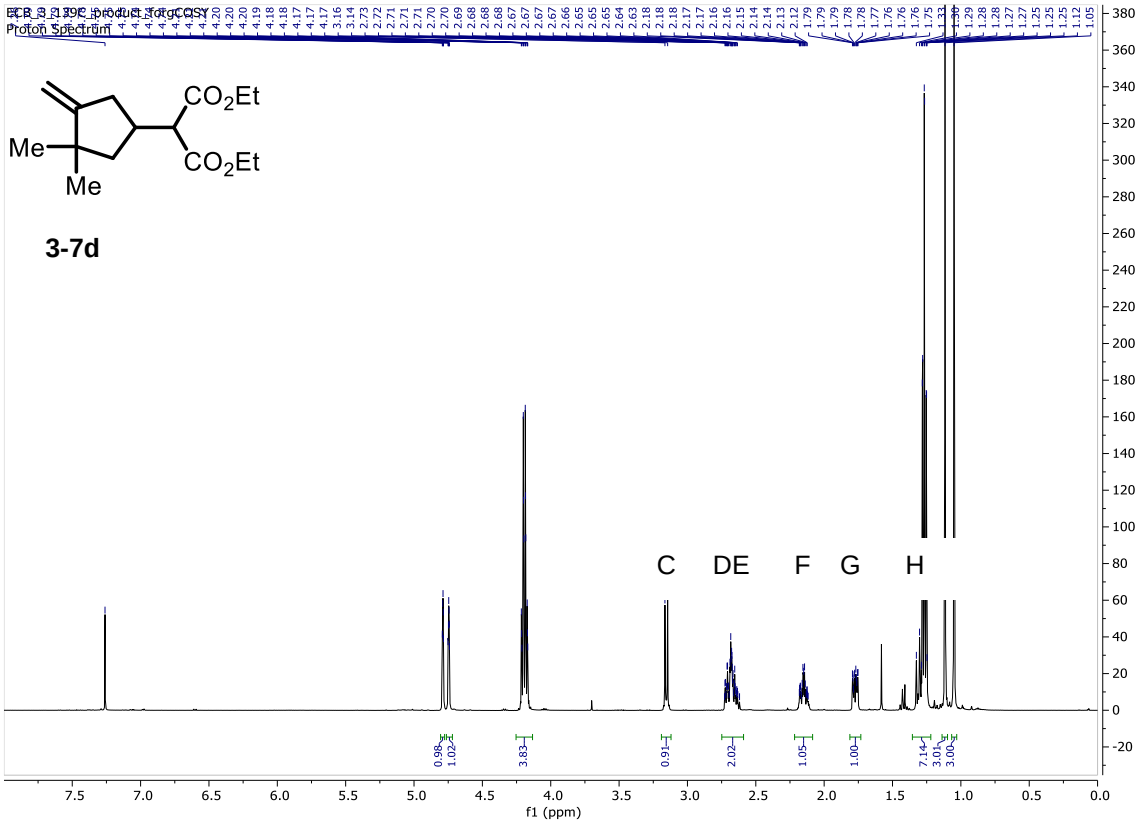
Diethyl 2-(3-methylene-4-oxocyclopentyl)malonate (3-S37) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with pyridinium p-toluenesulfonate (0.06 mmol, 15.1 mg, 1 equiv). **diethyl 2-(3,3-dimethoxy-4-methylenecyclopentyl)malonate (3-7c)** (0.06 mmol, 17.9 mg, 1 equiv) was dissolved in THF (0.6 mL, 0.1 M) and water (0.6 mL, 0.1 M) and added to the flask. The reaction was heated to 50 °C and stirred overnight (15 h). The reaction was cooled to rt then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 1 mL). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 12.1 mg (80%) of the title compound as a light yellow oil.

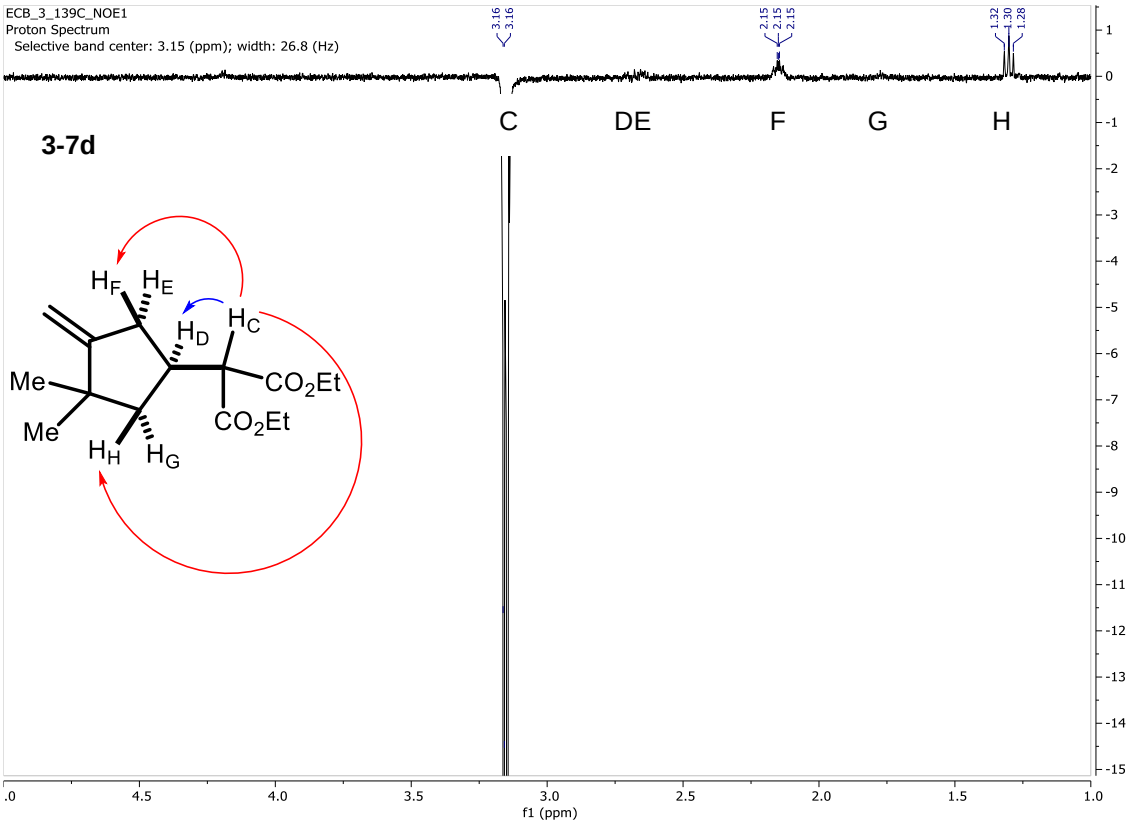
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05–5.97 (m, 1 H) 5.39–5.29 (m, 1 H) 4.28–4.15 (m, 4 H) 3.35 (d, *J* = 9.0 Hz, 1 H) 2.96 (dd, *J* = 16.3, 7.2 Hz, 1 H) 2.93–2.81 (m, 1 H) 2.62 (dd, *J* = 18.2, 7.7 Hz, 1 H) 2.47 (ddt, *J* = 15.8, 9.1, 3.0 Hz, 1 H) 2.24 (dd, *J* = 18.2, 9.8 Hz, 1 H) 1.34–1.23 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.34, 168.02, 167.96, 143.46, 117.90, 61.64, 61.63, 56.39, 42.75, 34.26, 33.10, 14.07, 14.05; IR (film) 2986, 2916, 2847, 1741, 1725, 1641 cm^{-1}; HRMS (ESI$^+$ TOF) m/z: $[M + Na^+]^+$ calcd for $C_{13}H_{18}O_5$ 277.1046; found 277.1042.

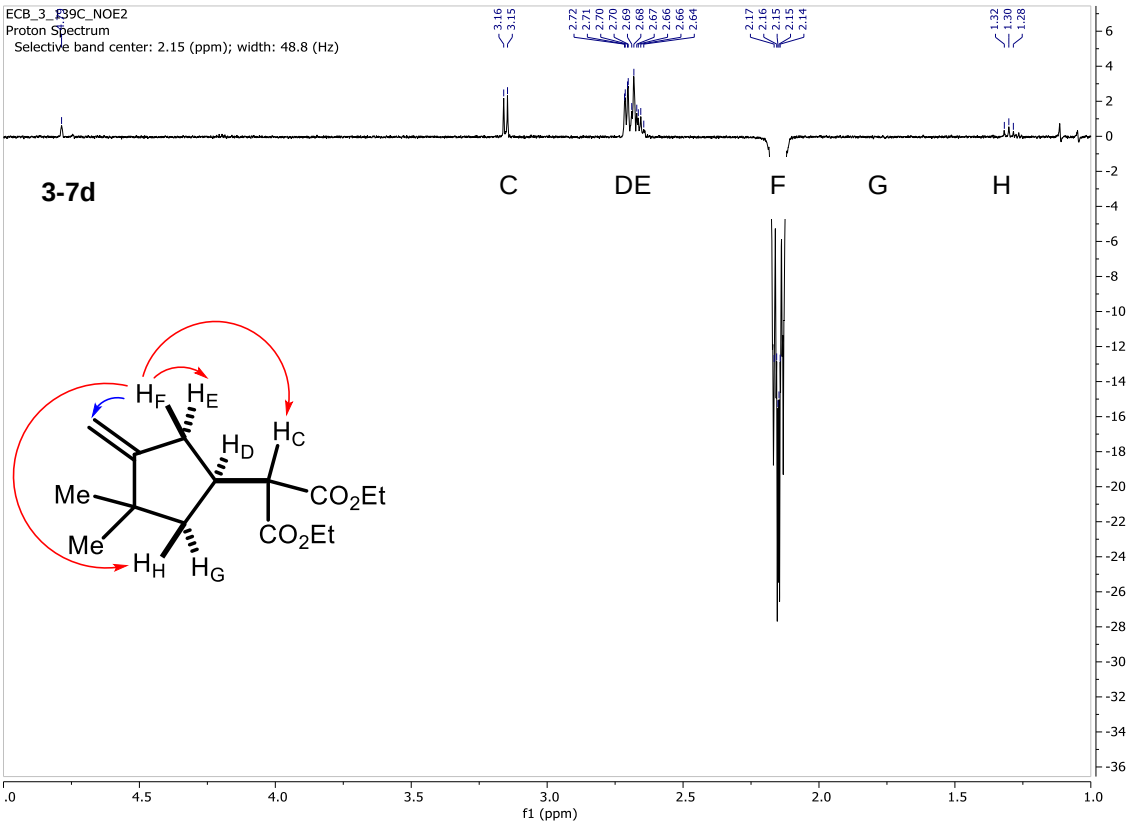
3.12 Assignment of Relative Stereochemistry

The relative stereochemistry of products **3-7d**, **3-17**, **3-S24**, **3-S25**, **3-S28**, **3-S29**, **3-S33**, **3-15**, was assigned on the basis of ^{1}H NMR nOe studies along with J coupling constant values. The data for these studies is provided below, along with the key nOe signals. The relative stereochemistry of all other products was assigned based on analogy to **3-S24**,

3-S25, **3-S28**, **3-S29**. The red arrows are for strong nOe correlations and the blue arrows are for lesser nOe correlations.




ECB_3_139C_NOE1
Proton Spectrum
Selective band center: 3.15 (ppm); width: 26.8 (Hz)
3.16
3.16
2.15
2.15
2.15
1.32
1.30
1.28
C
DE
F
G
H
3-7d
HF
HE
HD
HC
Me
Me
CO2Et
CO2Et
HH
HG
f1 (ppm)


ECB_3_139C_NOE2
Proton Spectrum
Selective band center: 2.15 (ppm); width: 48.8 (Hz)
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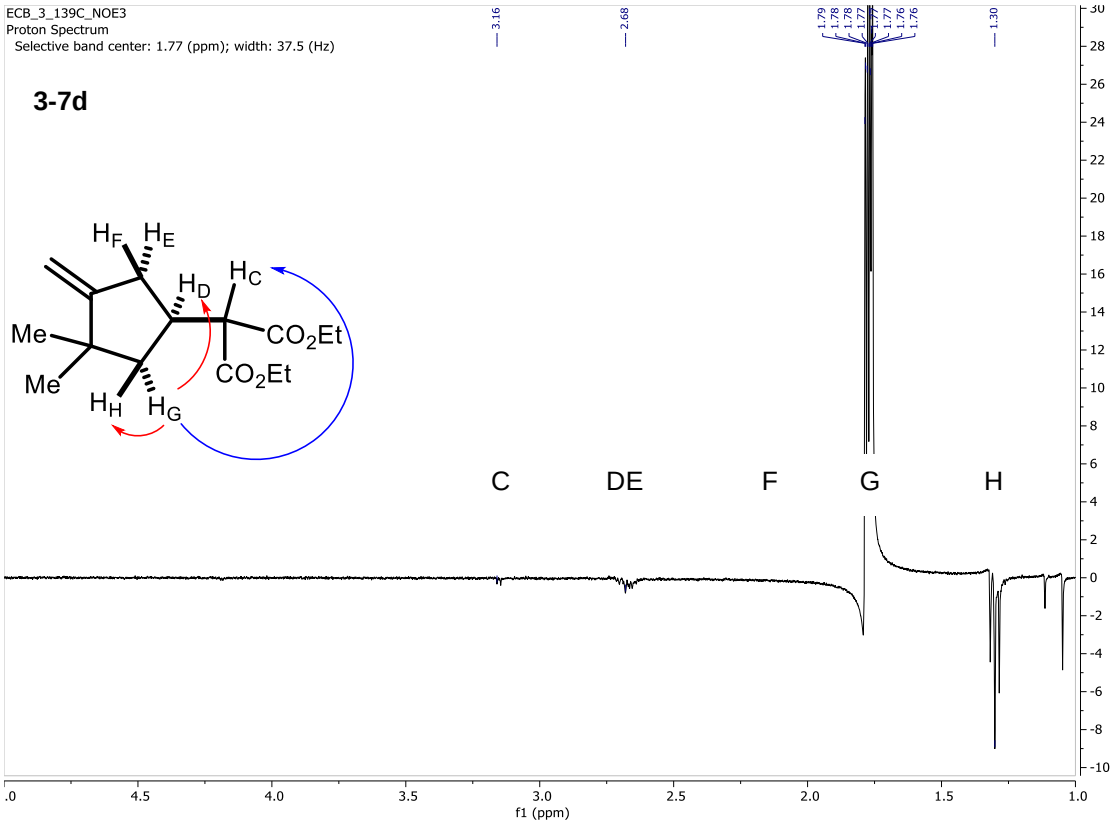
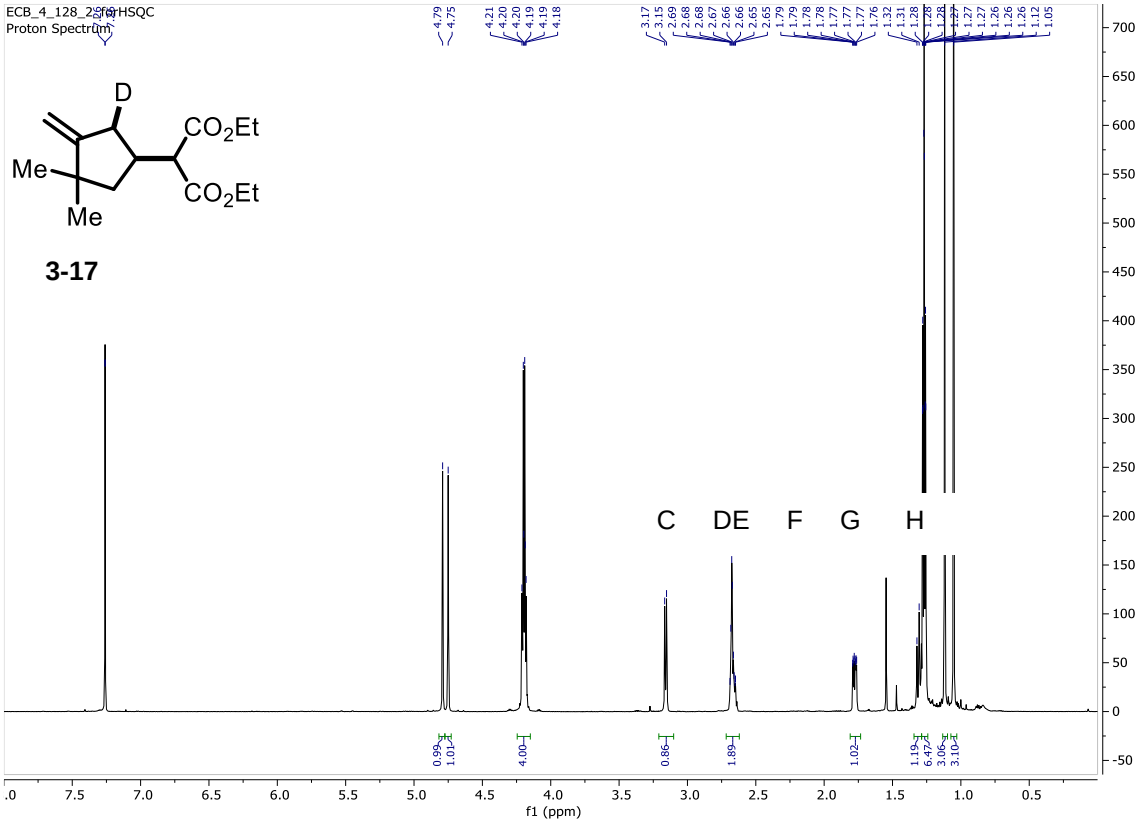
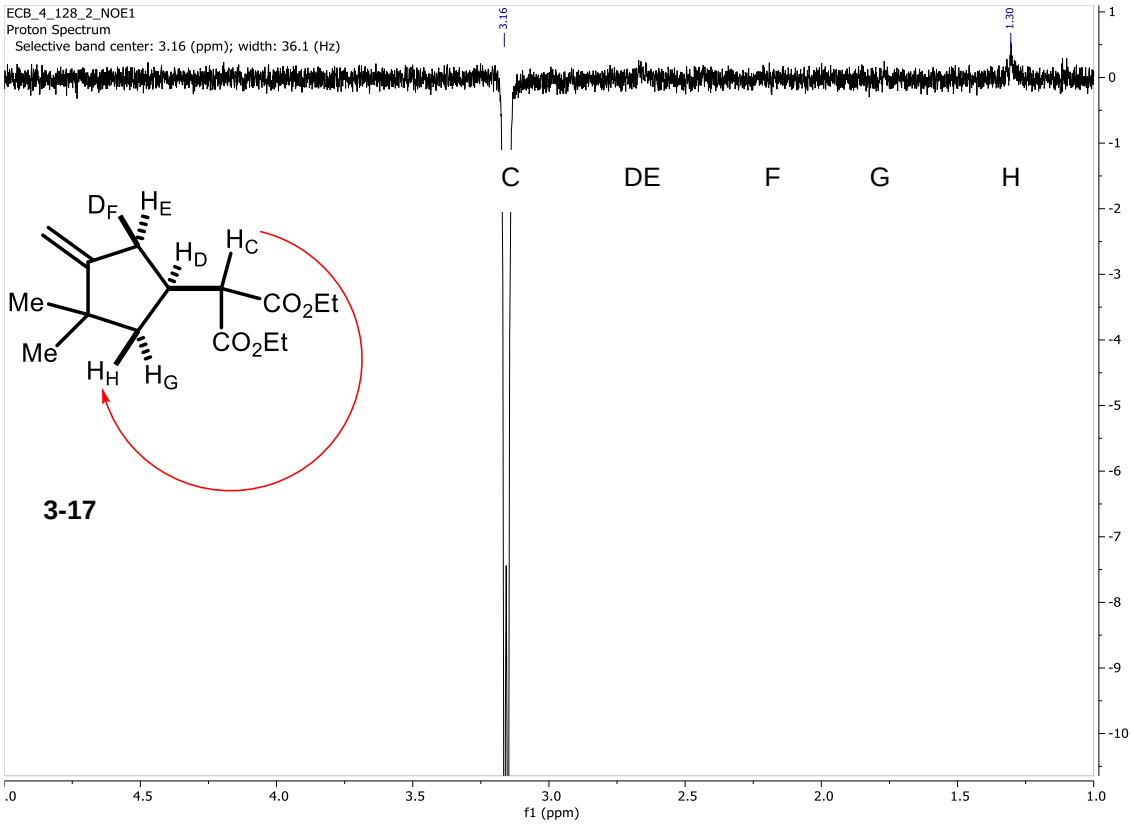
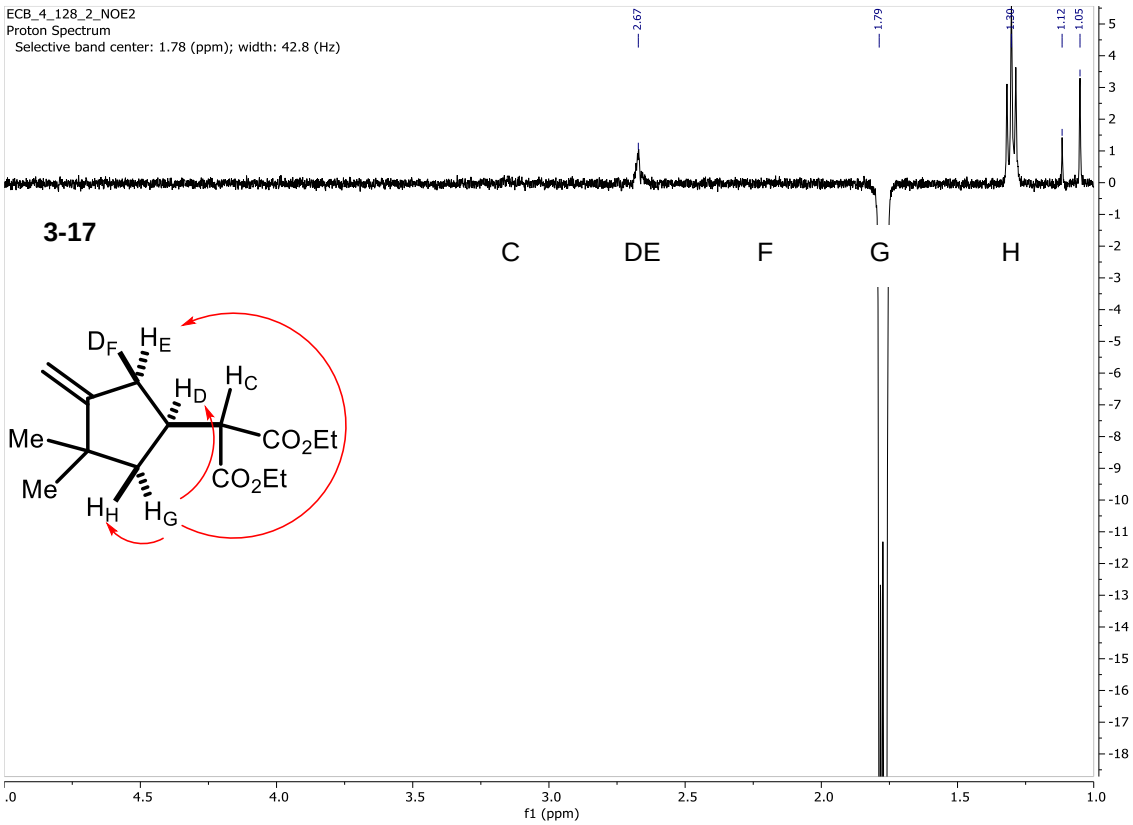
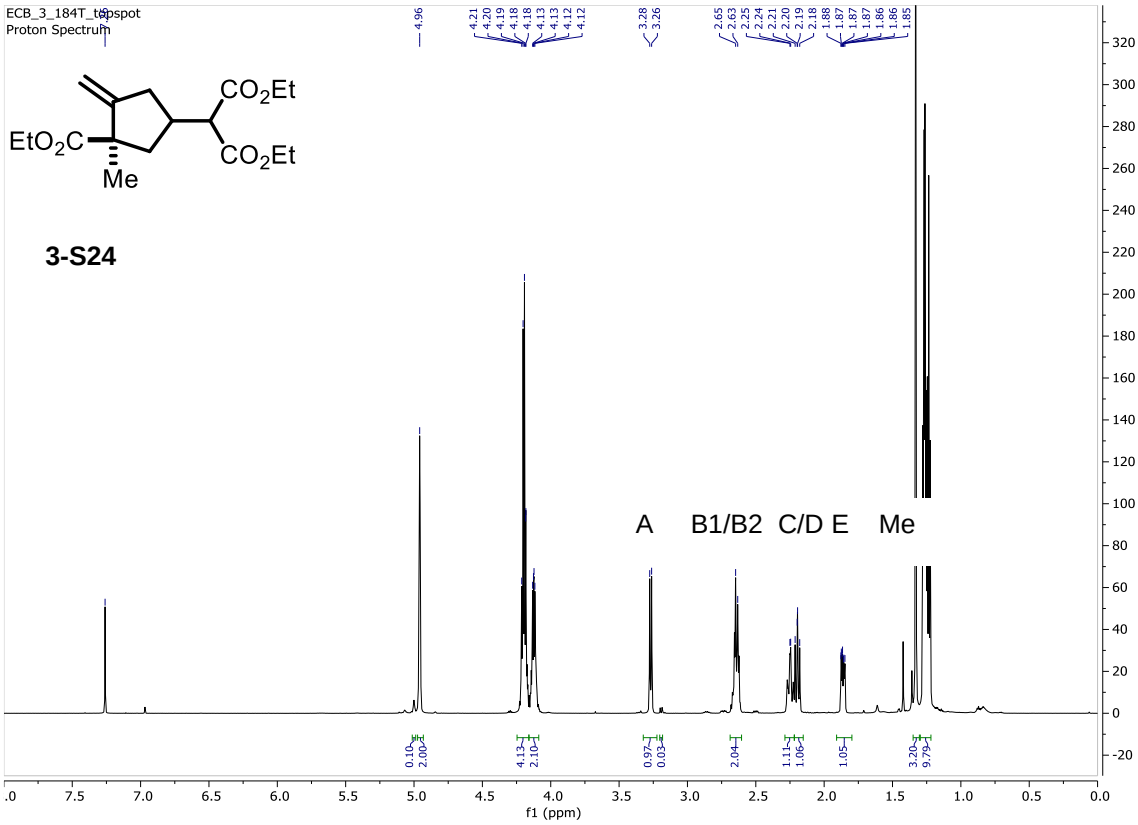
3.15
2.72
2.71
2.70
2.70
2.69
2.68
2.67
2.66
2.66
2.64
2.17
2.16
2.15
2.15
2.14
1.32
1.30
1.28
C
DE
F
G
H
3-7d
HF
HE
HD
HC
Me
Me
CO2Et
CO2Et
HH
HG
f1 (ppm)

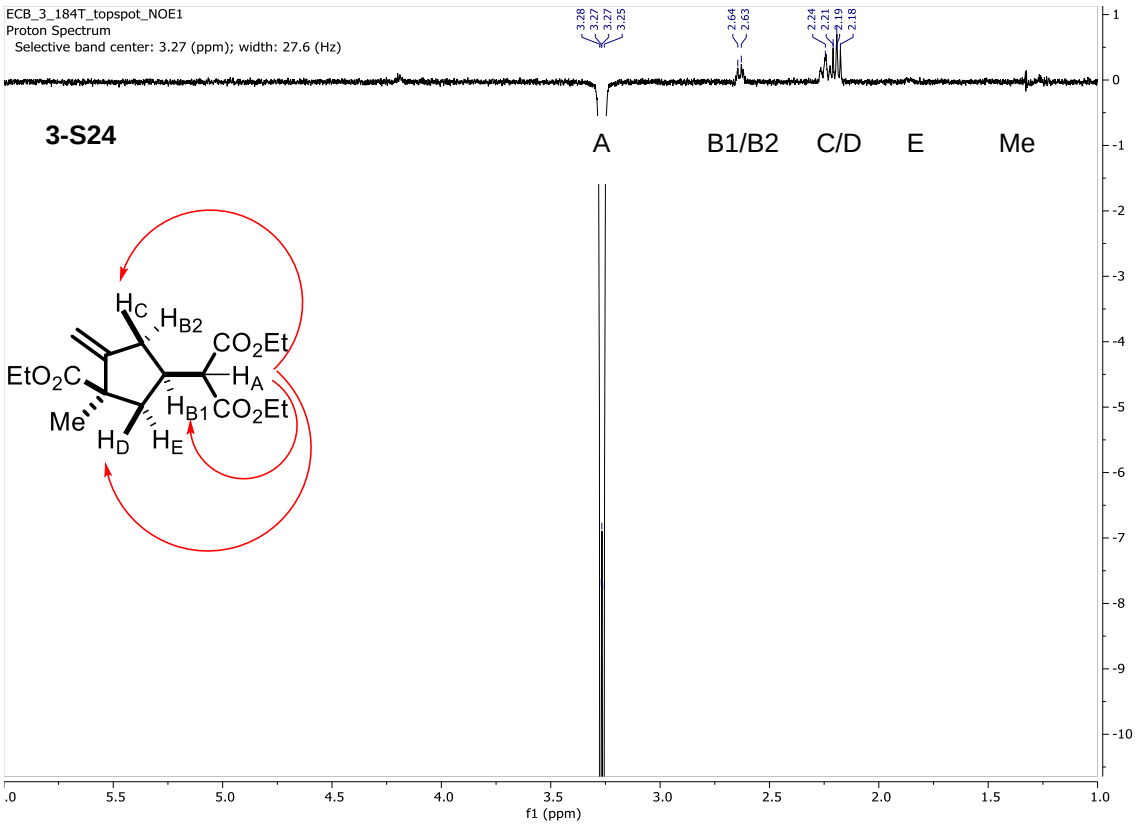

ECB_3_139C_NOE3
Proton Spectrum
Selective band center: 1.77 (ppm); width: 37.5 (Hz)
3-7d
Me
Me
CO2Et
CO2Et
C
DE
F
G
H
f1 (ppm)


Proton Spectrum
D
CO2Et
CO2Et
Me
Me
3-17
C
DE
F
G
H
f1 (ppm)


ECB_4_128_2_NOE1
Proton Spectrum
Selective band center: 3.16 (ppm); width: 36.1 (Hz)
3.16
1.30
C
DE
F
G
H
D_F
H_E
H_D
H_C
Me
CO2Et
Me
CO2Et
H_H
H_G
3-17
f1 (ppm)


ECB_4_128_2_NOE2
Proton Spectrum
Selective band center: 1.78 (ppm); width: 42.8 (Hz)
2.67
1.79
1.30
1.12
1.05
3-17
C
DE
F
G
H
D_F
H_E
H_D
H_C
Me
CO2Et
Me
CO2Et
H_H
H_G
f1 (ppm)


ECB_3_184T_topspot
Proton Spectrum
CO2Et
EtO2C
CO2Et
Me
3-S24
A
B1/B2
C/D
E
Me
f1 (ppm)


ECB_3_184T_topspot_NOE1
Proton Spectrum
Selective band center: 3.27 (ppm); width: 27.6 (Hz)
3-S24
A
B1/B2
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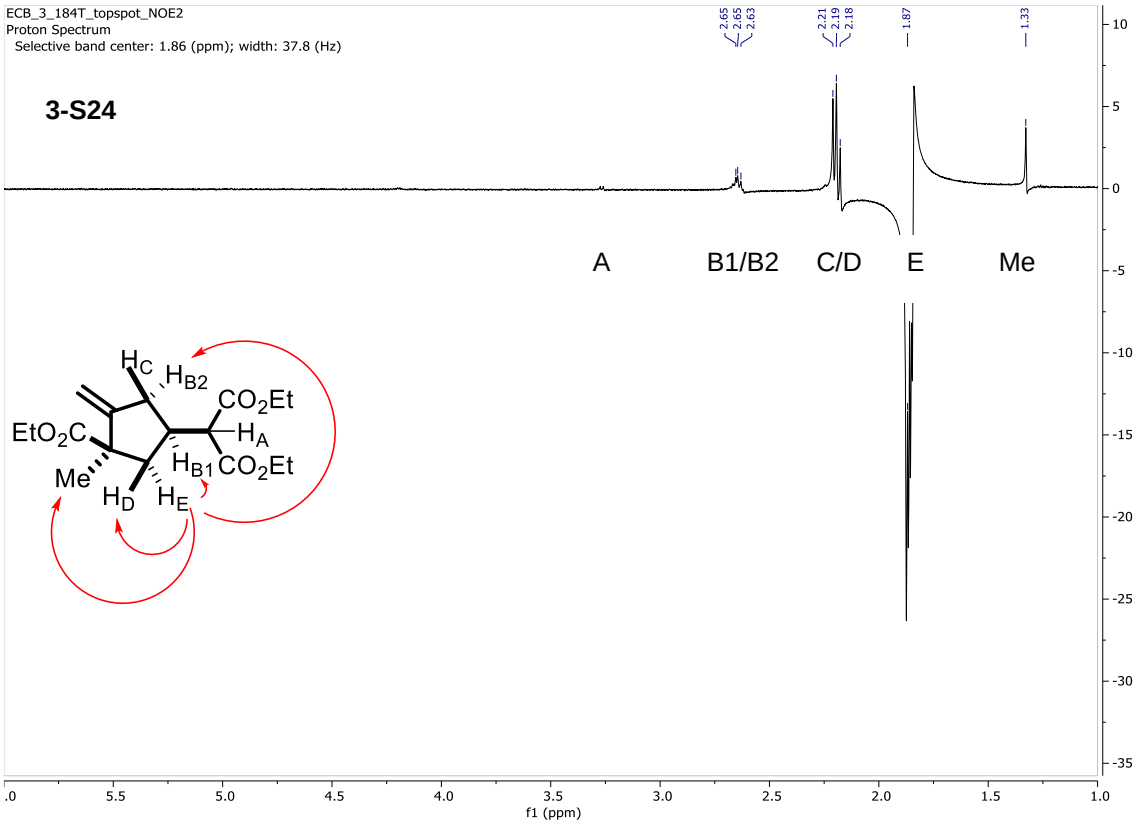
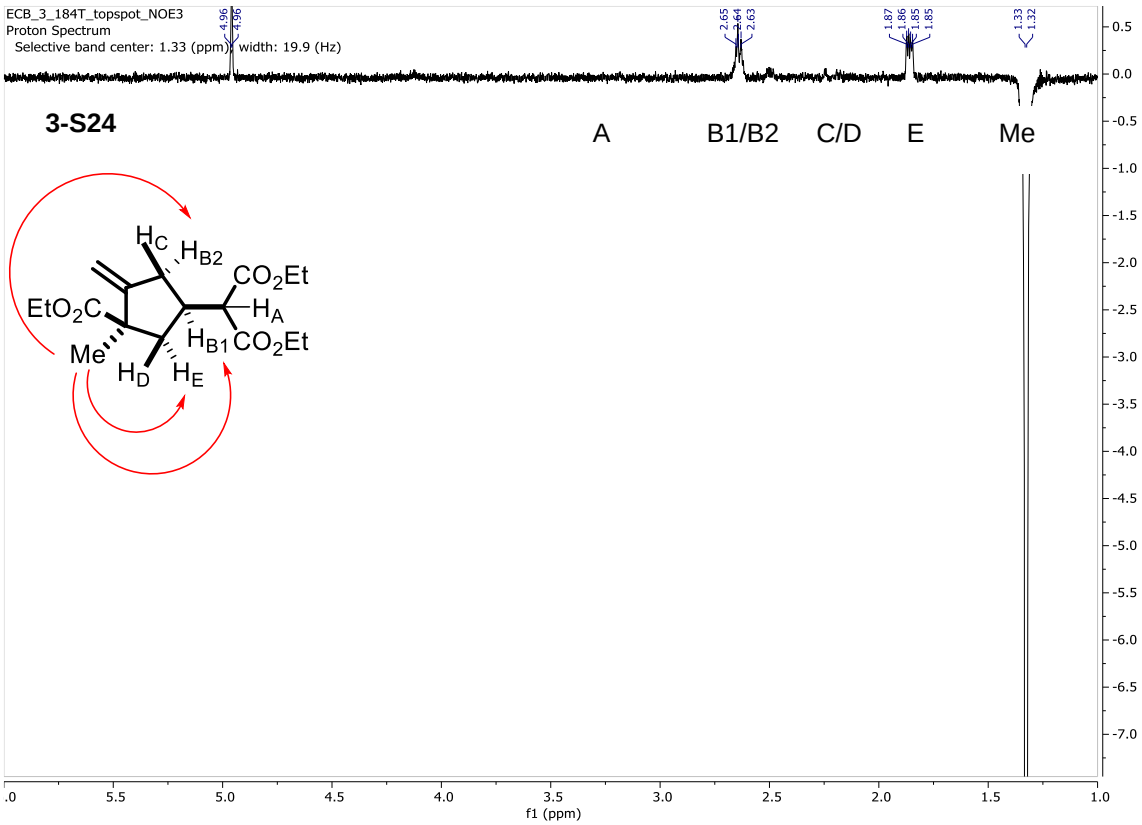
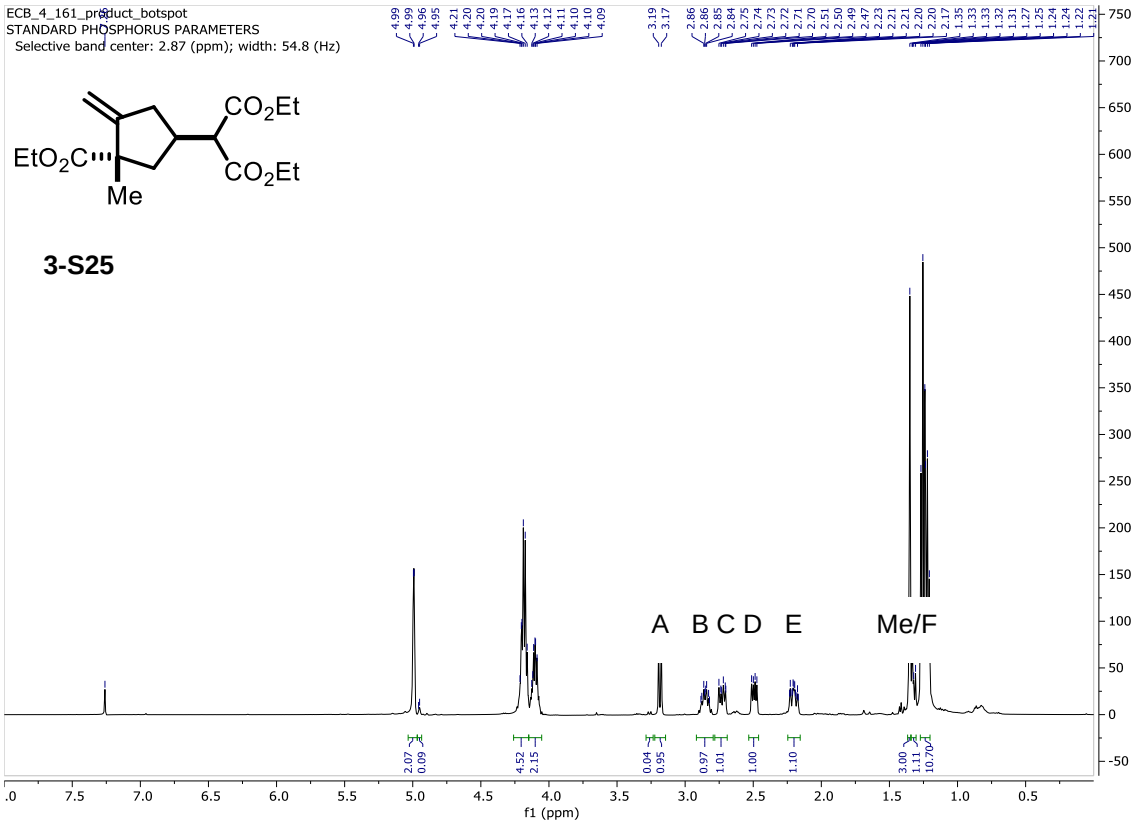
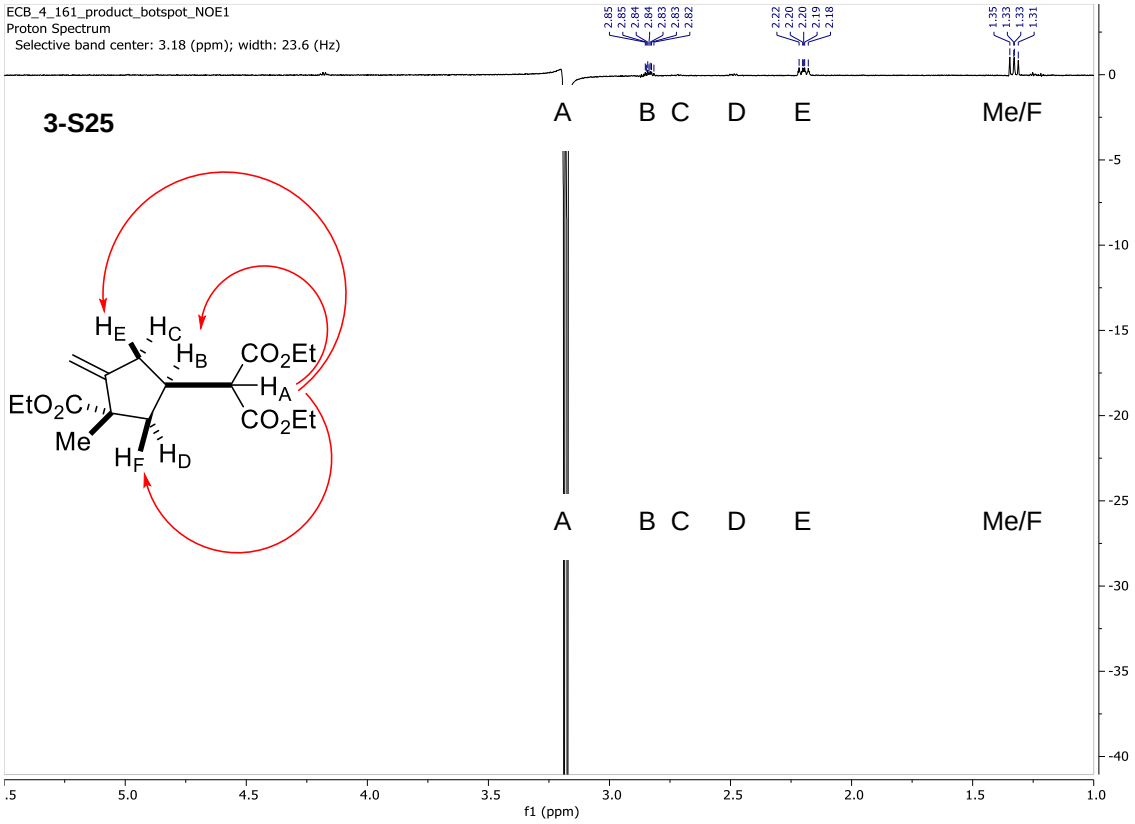
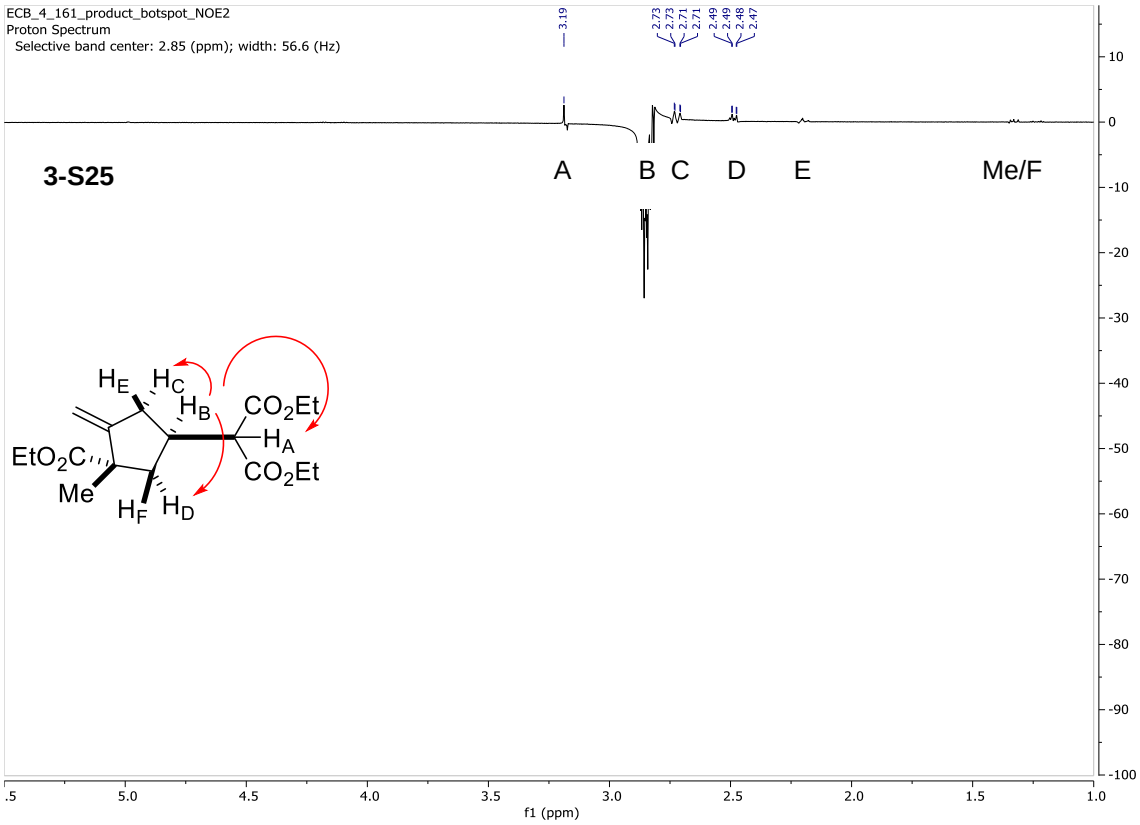
HA
HB1
CO2Et
Me
HD
HE
f1 (ppm)

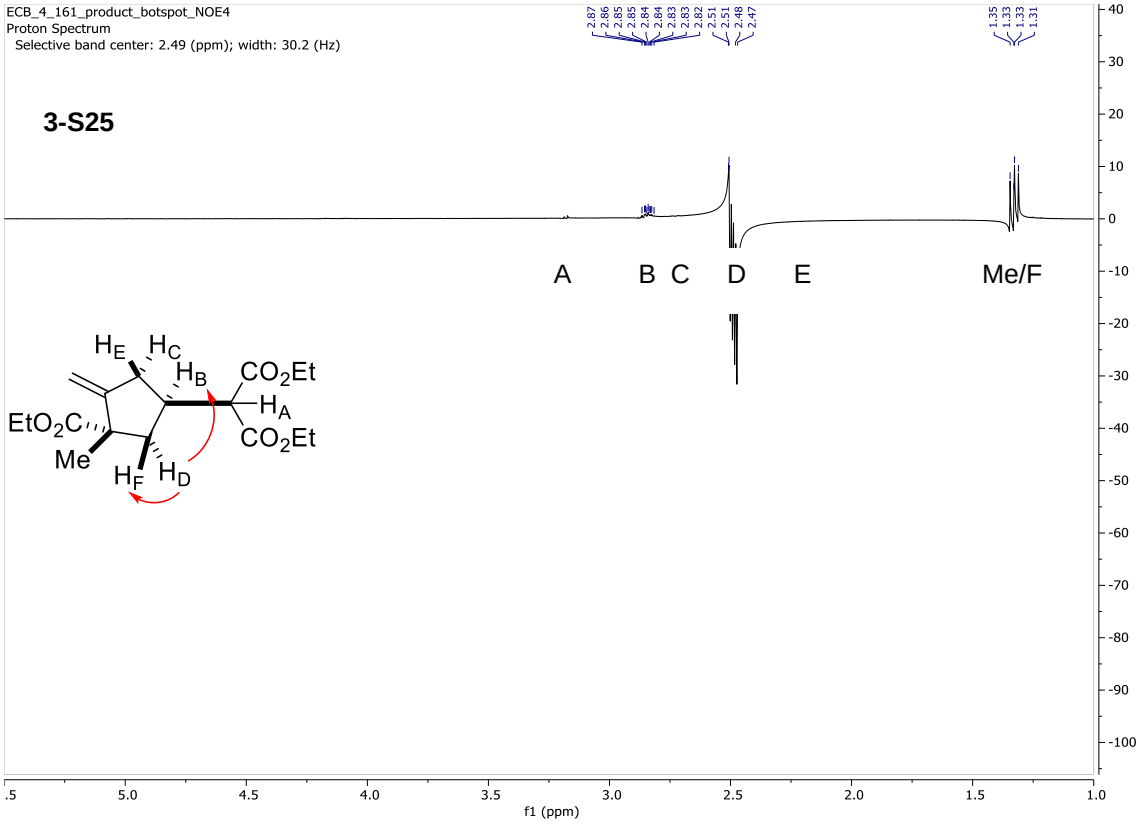

ECB_3_184T_topspot_NOE2
Proton Spectrum
Selective band center: 1.86 (ppm); width: 37.8 (Hz)
3-S24
A
B1/B2
C/D
E
Me
f1 (ppm)

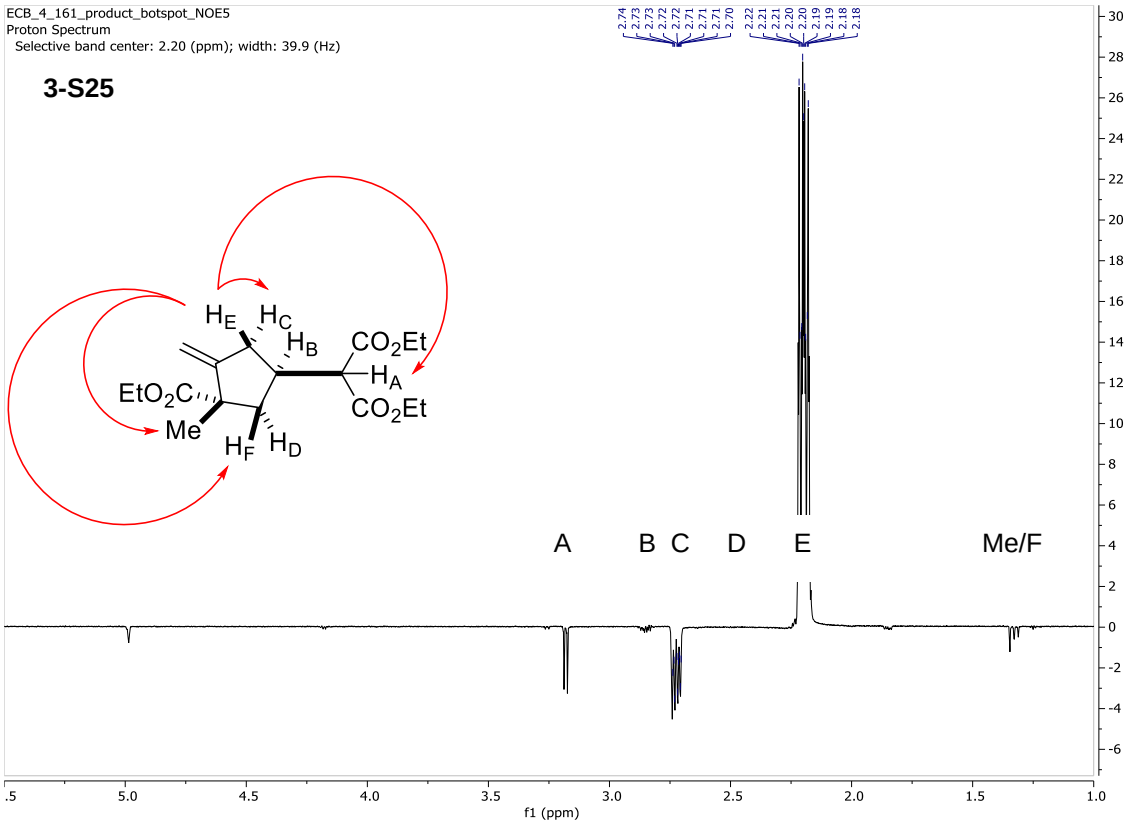

ECB_3_184T_topspot_NOE3
Proton Spectrum
Selective band center: 1.33 (ppm); width: 19.9 (Hz)
3-S24
A
B1/B2
C/D
E
Me
f1 (ppm)

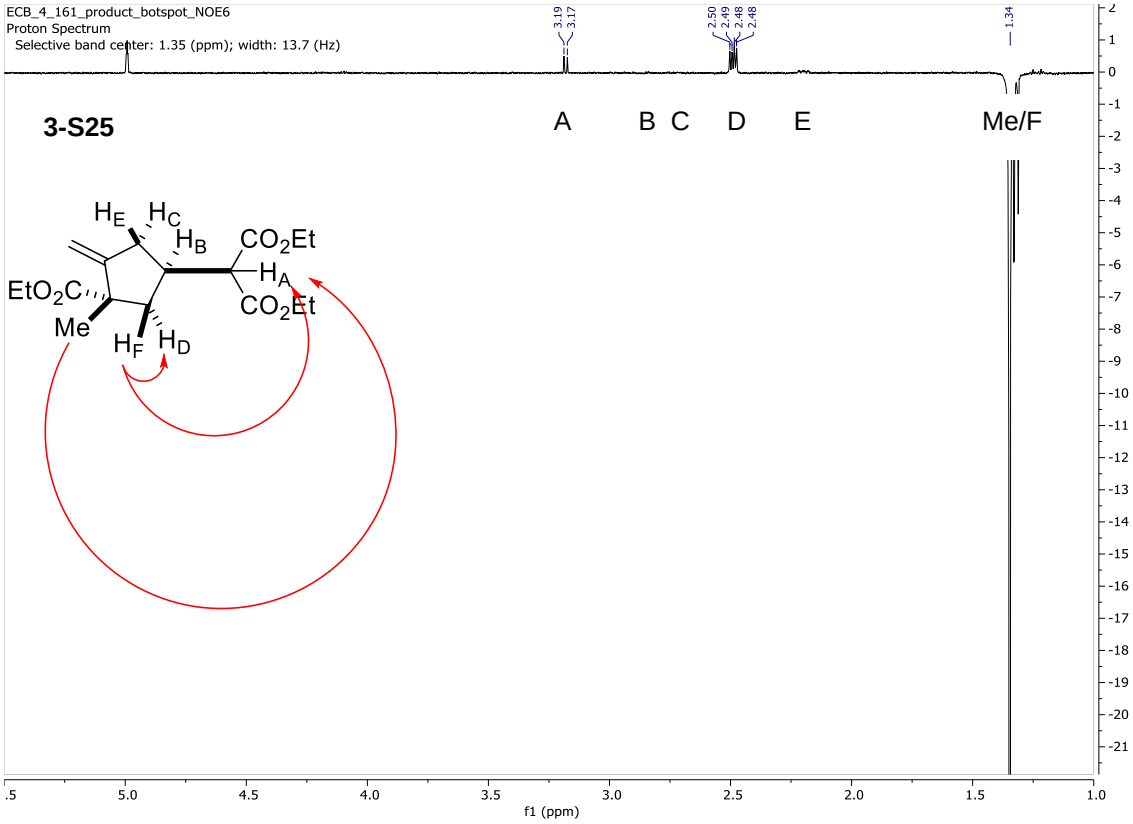

ECB_4_161_product_botspot
STANDARD PHOSPHORUS PARAMETERS
Selective band center: 2.87 (ppm); width: 54.8 (Hz)
CO2Et
EtO2C
CO2Et
Me
3-S25
A B C D E
Me/F
f1 (ppm)

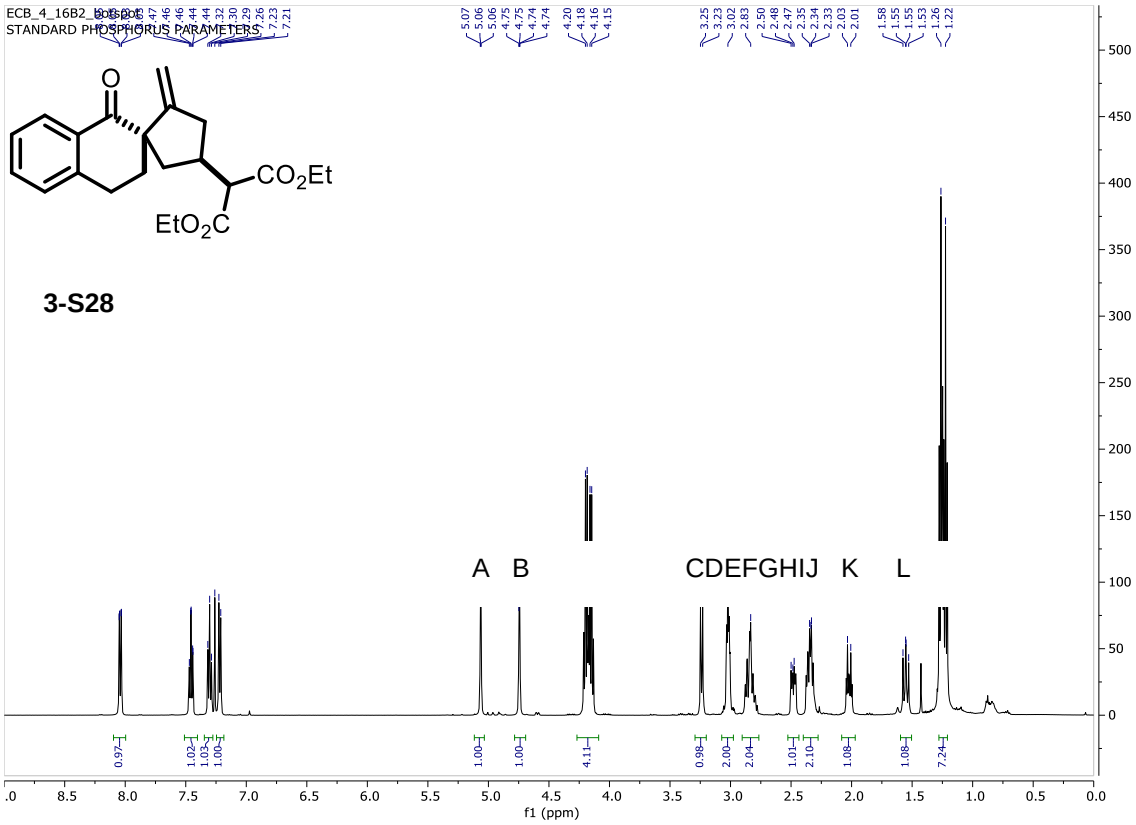

ECB_4_161_product_botspot_NOE1
Proton Spectrum
Selective band center: 3.18 (ppm); width: 23.6 (Hz)
3-S25
A B C D E
Me/F
HE HC HB
CO2Et
HA
EtO2C
CO2Et
Me
HF HD
A B C D E
Me/F
f1 (ppm)

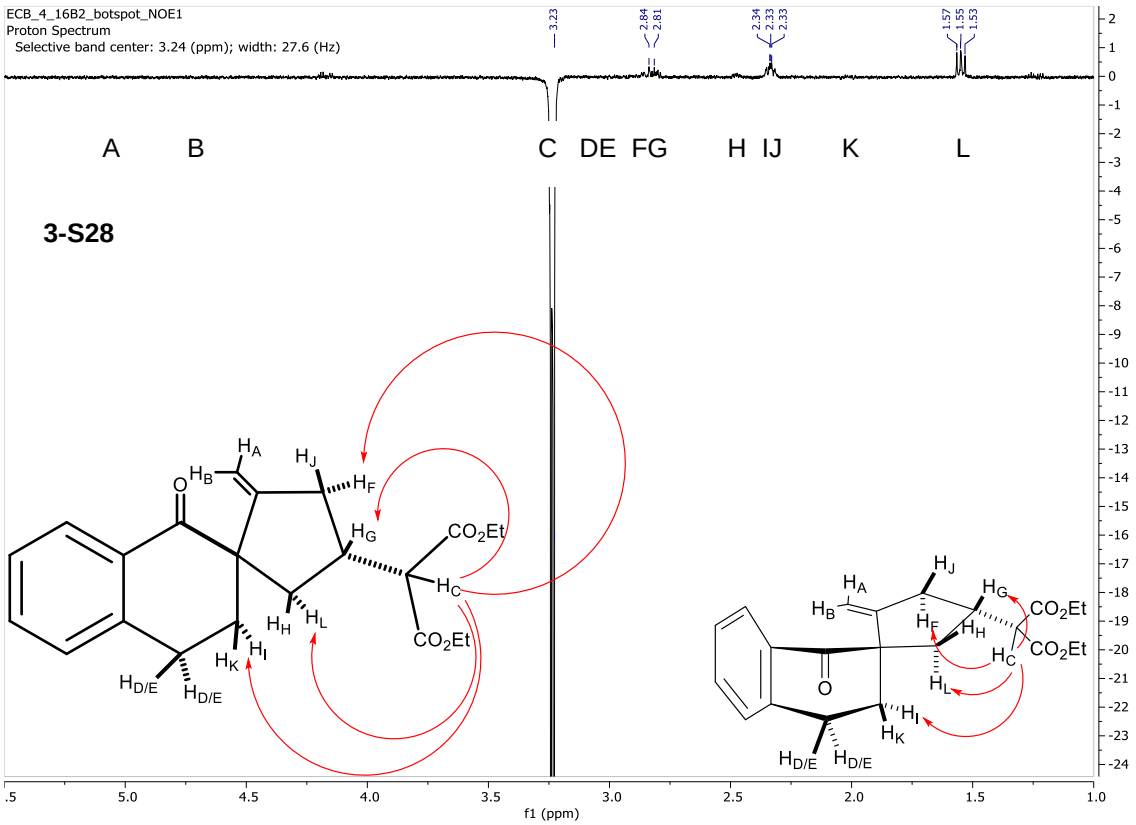

ECB_4_161_product_botspot_NOE2
Proton Spectrum
Selective band center: 2.85 (ppm); width: 56.6 (Hz)
3.19
2.73
2.73
2.71
2.71
2.49
2.49
2.48
2.47
3-S25
A
B C
D
E
Me/F
HE HC
HB
CO2Et
HA
EtO2C
CO2Et
Me
HF HD
f1 (ppm)

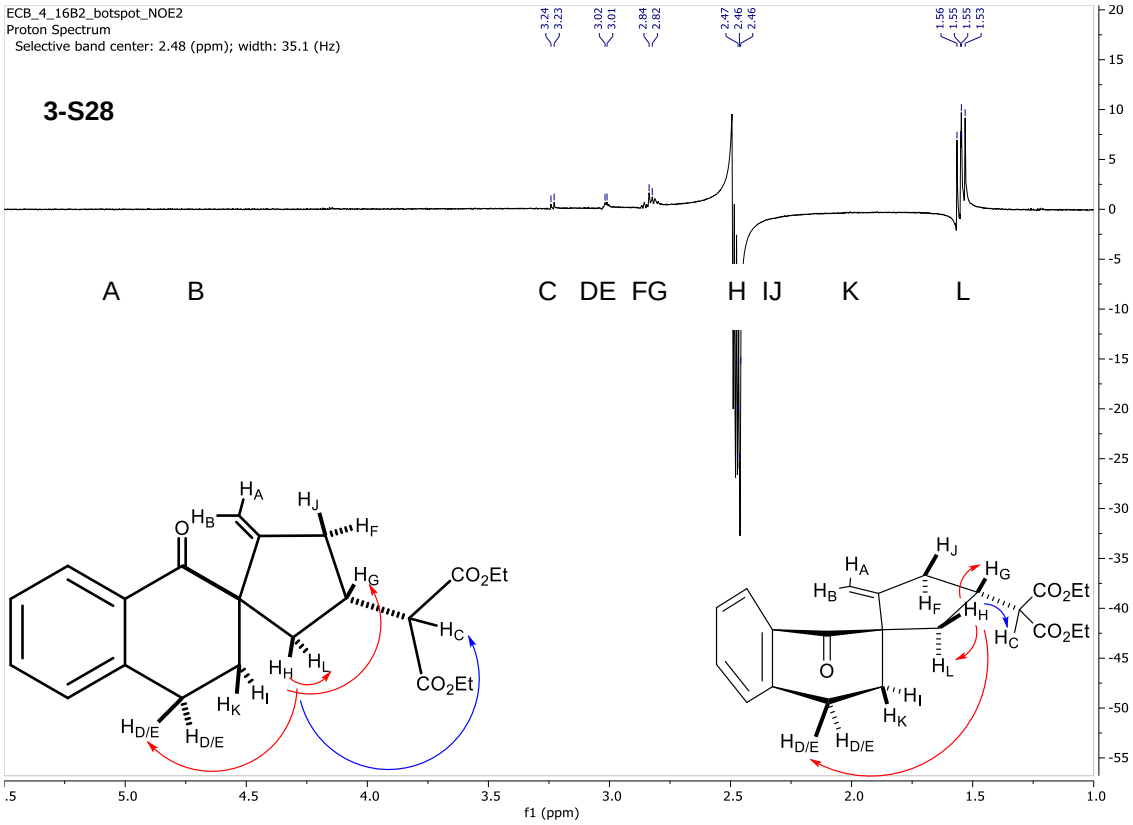

ECB_4_161_product_botspot_NOE4
Proton Spectrum
Selective band center: 2.49 (ppm); width: 30.2 (Hz)
2.87
2.86
2.85
2.85
2.84
2.84
2.83
2.83
2.82
2.51
2.51
2.48
2.47
1.35
1.33
1.33
1.31
3-S25
A
B C
D
E
Me/F
HE HC
HB
CO2Et
HA
EtO2C
CO2Et
Me
HF HD
f1 (ppm)

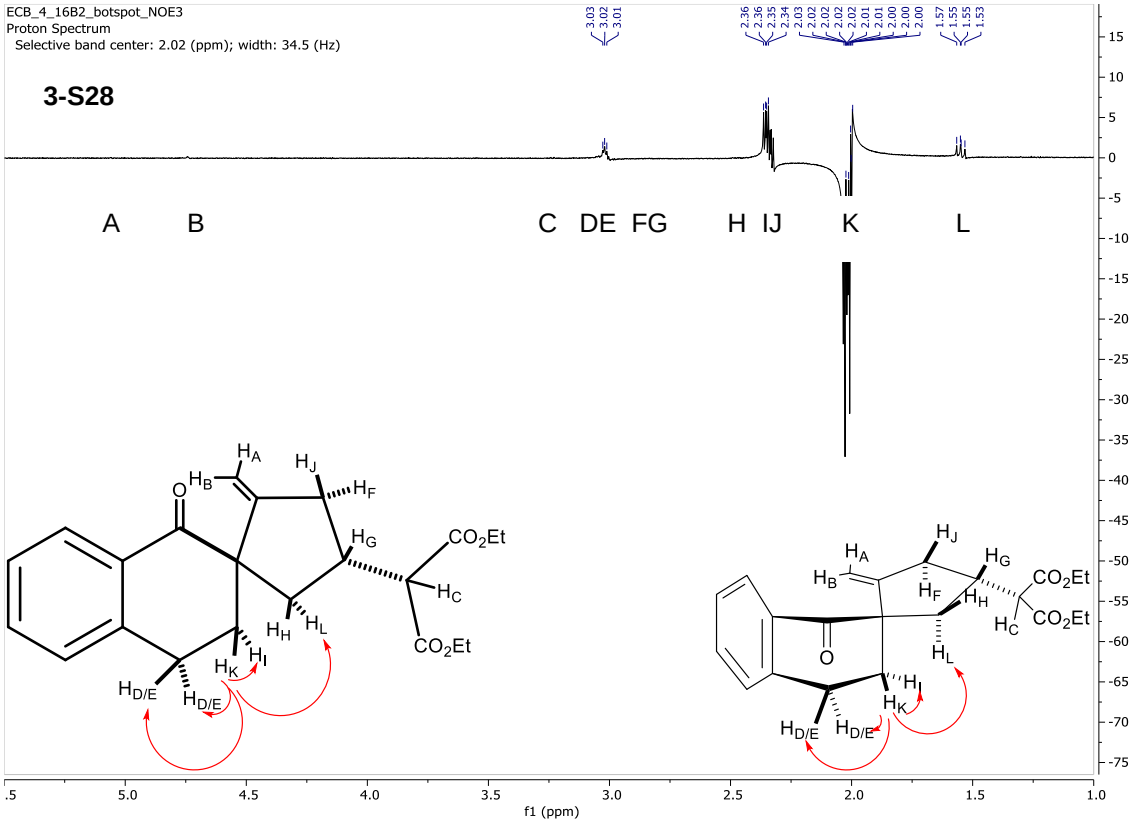

ECB_4_161_product_botspot_NOE5
Proton Spectrum
Selective band center: 2.20 (ppm); width: 39.9 (Hz)
3-S25
A
B C
D
E
Me/F
f1 (ppm)

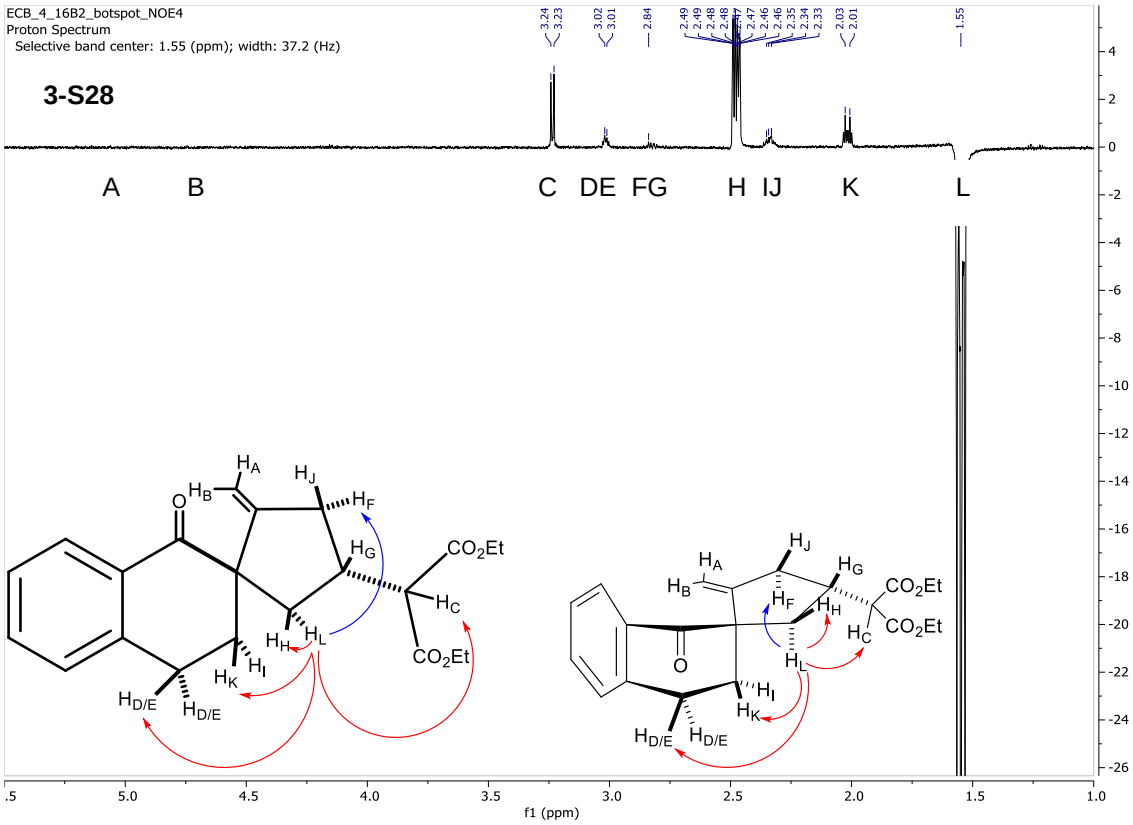

ECB_4_161_product_botspot_NOE6
Proton Spectrum
Selective band center: 1.35 (ppm); width: 13.7 (Hz)
3-S25
A
B C
D
E
Me/F
f1 (ppm)

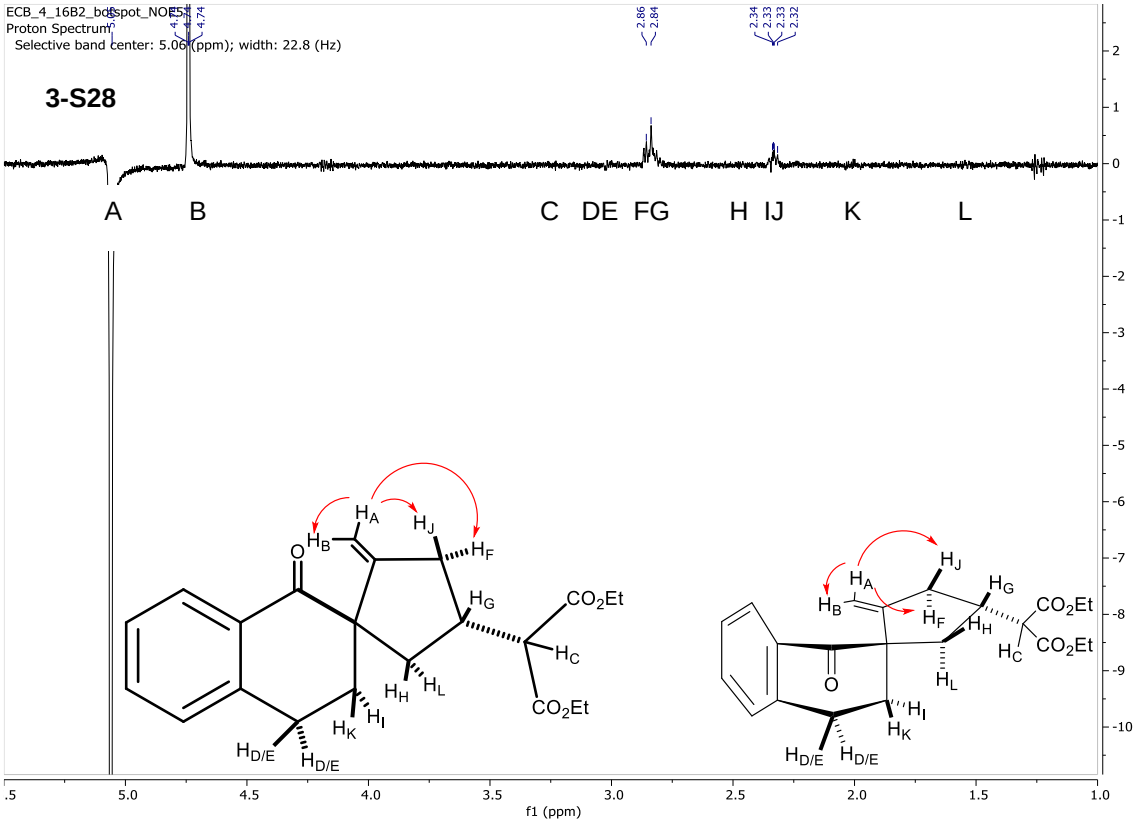

ECB_4_16B2_botspot
STANDARD PHOSPHORUS PARAMETERS
O
CO2Et
EtO2C
3-S28
A B CDEFGHIJ K L
f1 (ppm)

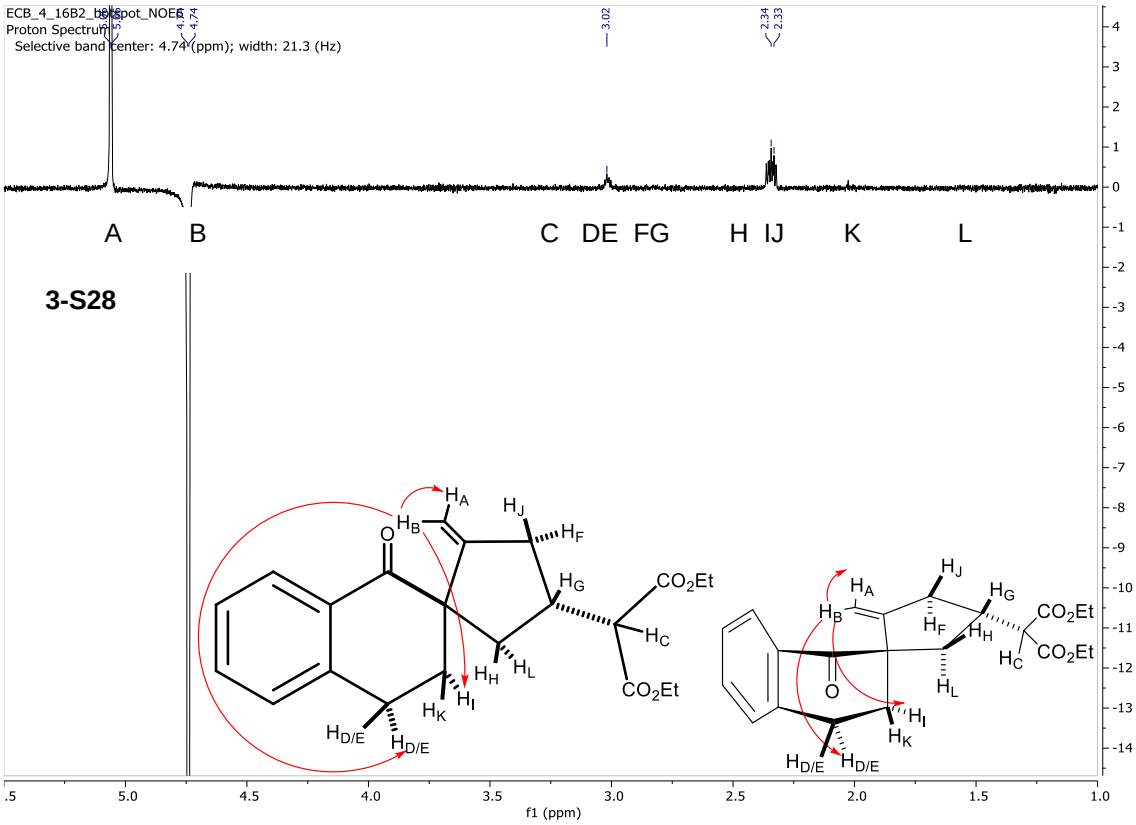

ECB_4_16B2_botspot_NOE1
Proton Spectrum
Selective band center: 3.24 (ppm); width: 27.6 (Hz)
A B C DE FG H IJ K L
3-S28
HA
HB
HC
HD/E
HF
HG
HH
HI
HJ
HK
HL
CO2Et
f1 (ppm)

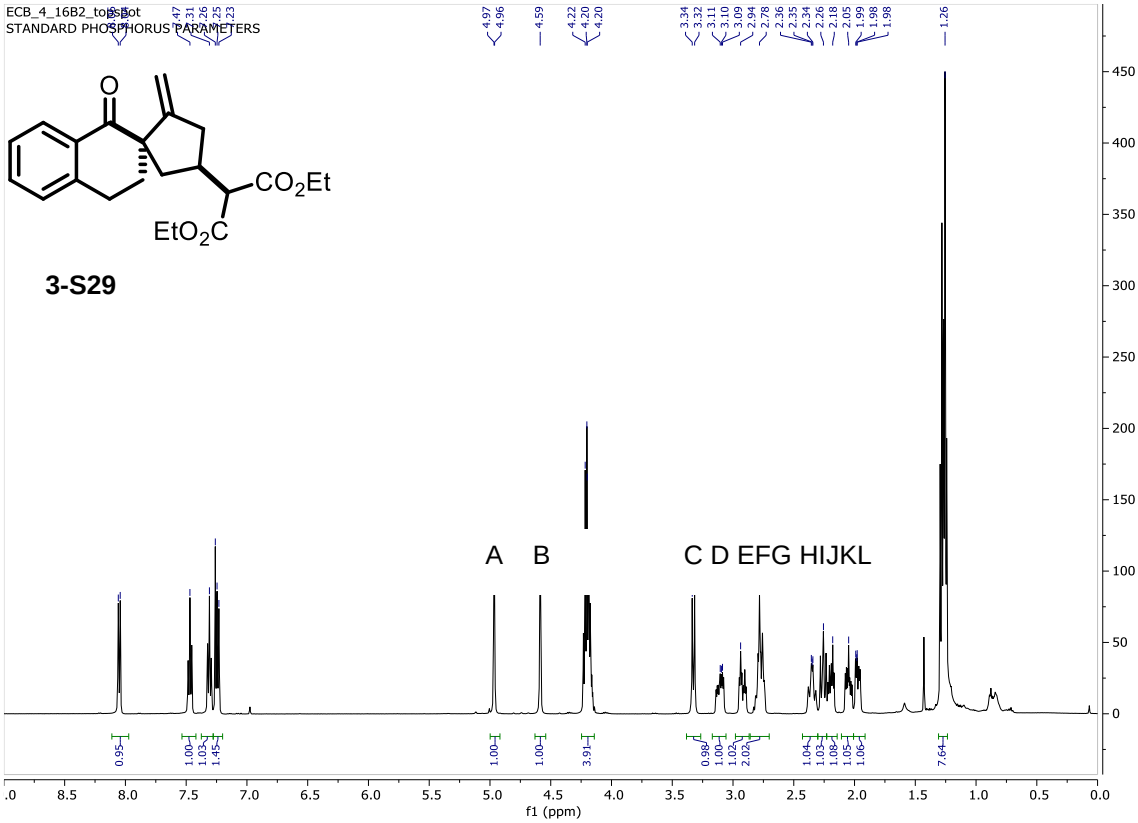

ECB_4_16B2_botspot_NOE2
Proton Spectrum
Selective band center: 2.48 (ppm); width: 35.1 (Hz)
3-S28
A B C DE FG H IJ K L
f1 (ppm)

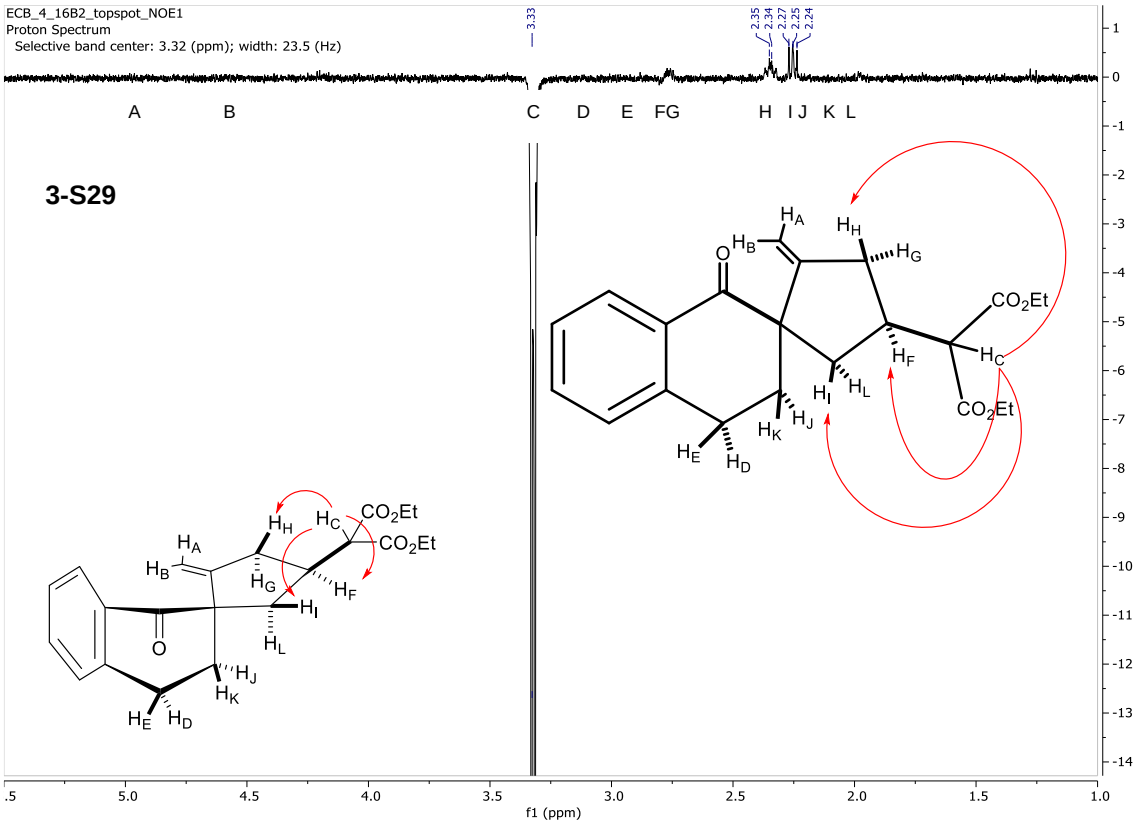

ECB_4_16B2_botspot_NOE3
Proton Spectrum
Selective band center: 2.02 (ppm); width: 34.5 (Hz)
3-S28
A B C DE FG H IJ K L
f1 (ppm)

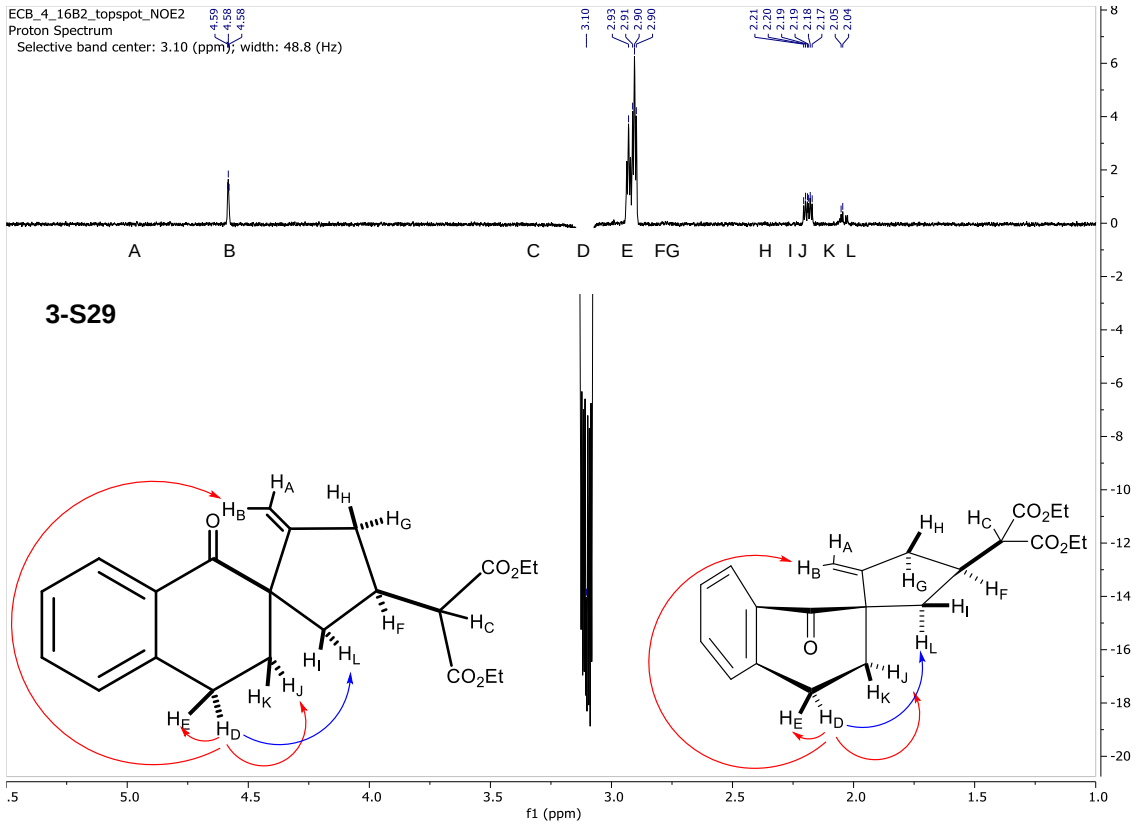

ECB_4_16B2_botspot_NOE4
Proton Spectrum
Selective band center: 1.55 (ppm); width: 37.2 (Hz)
3-S28
A B C DE FG H IJ K L
f1 (ppm)

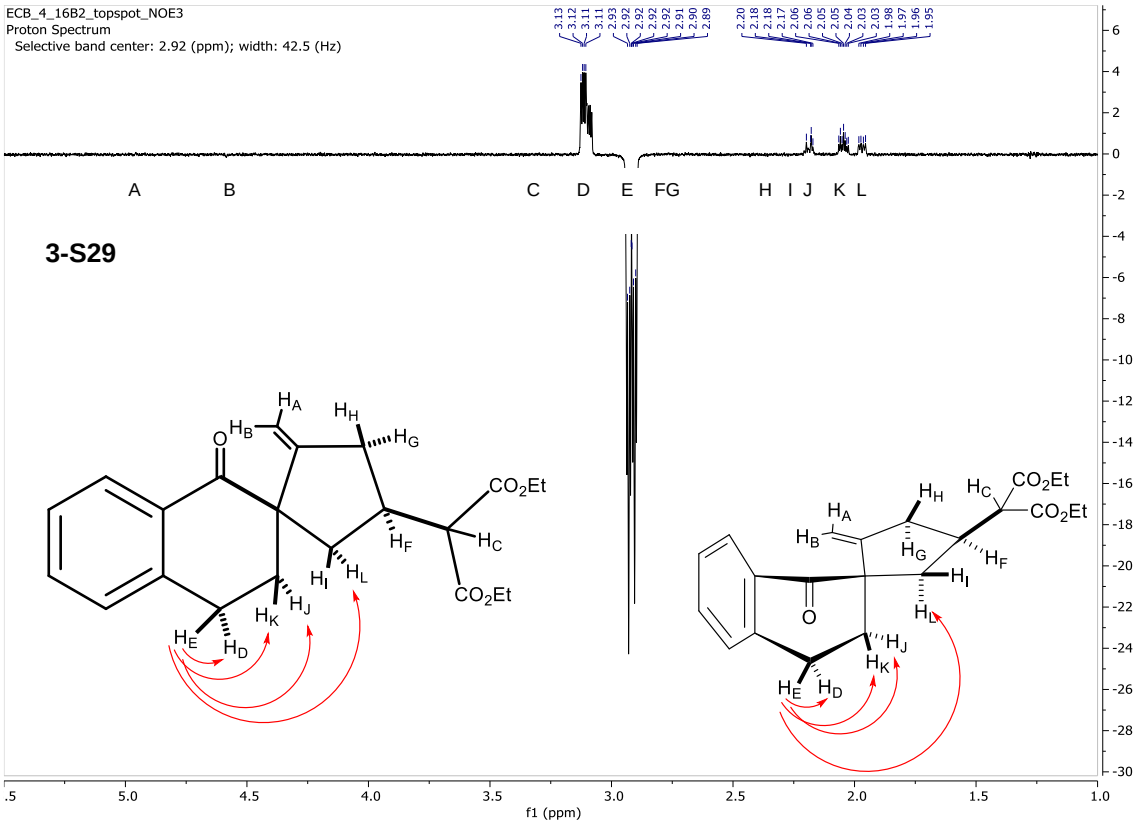

ECB_4_16B2_botspot_NOE5
Proton Spectrum
Selective band center: 5.06 (ppm); width: 22.8 (Hz)
3-S28
A B C DE FG H IJ K L
f1 (ppm)

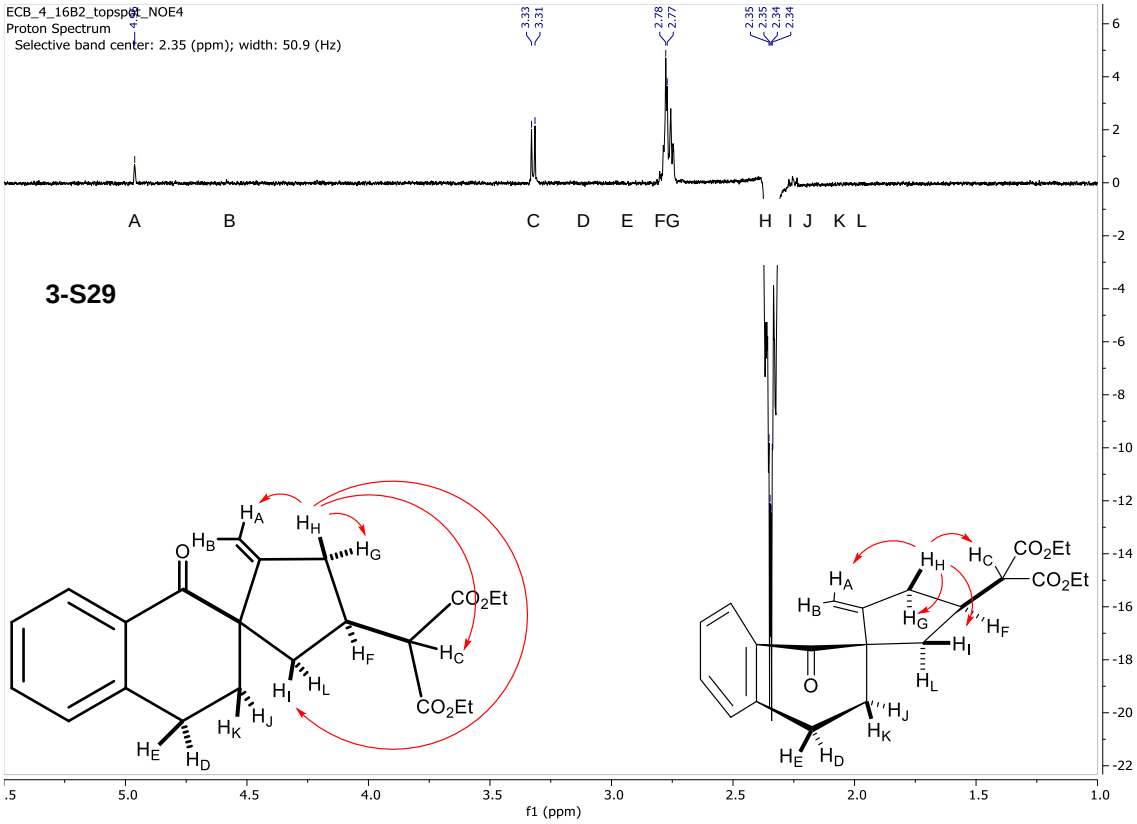

Proton Spectrum
Selective band center: 4.74 (ppm); width: 21.3 (Hz)
A B C DE FG H IJ K L
3-S28
f1 (ppm)

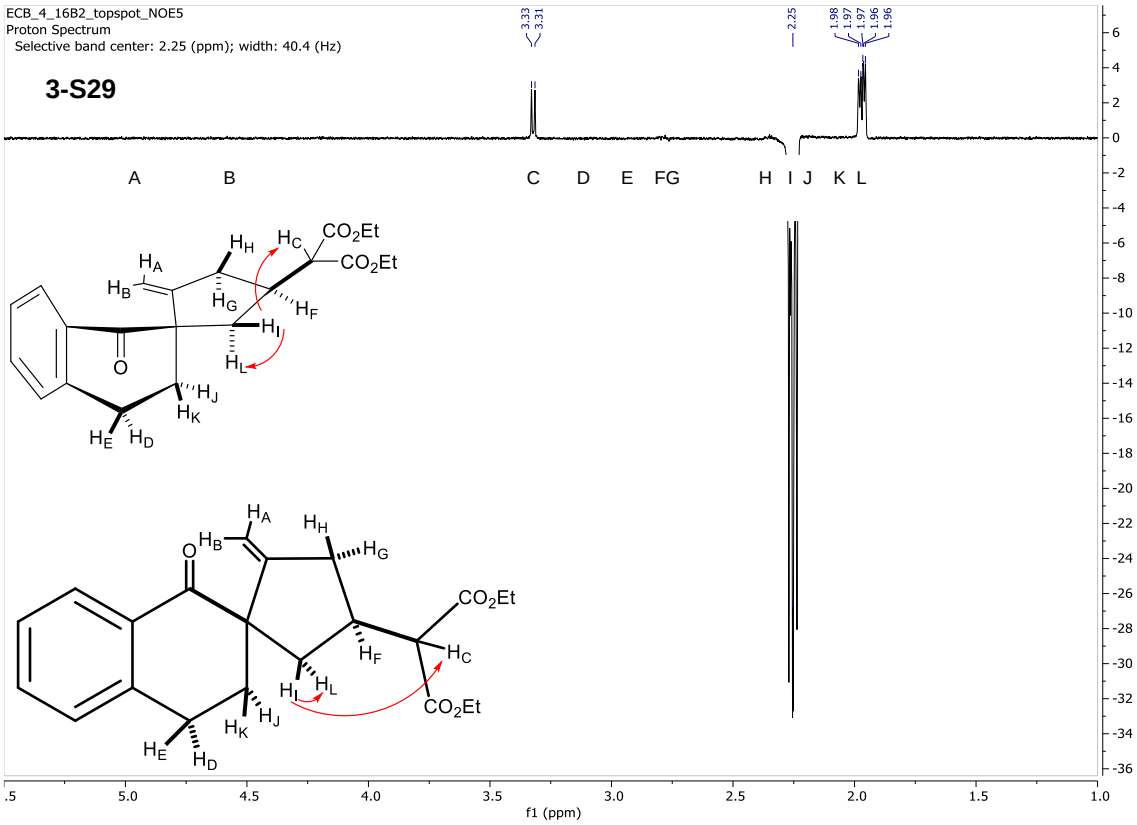

STANDARD PHOSPHORUS PARAMETERS
A B C D EFG HIJKL
3-S29
f1 (ppm)

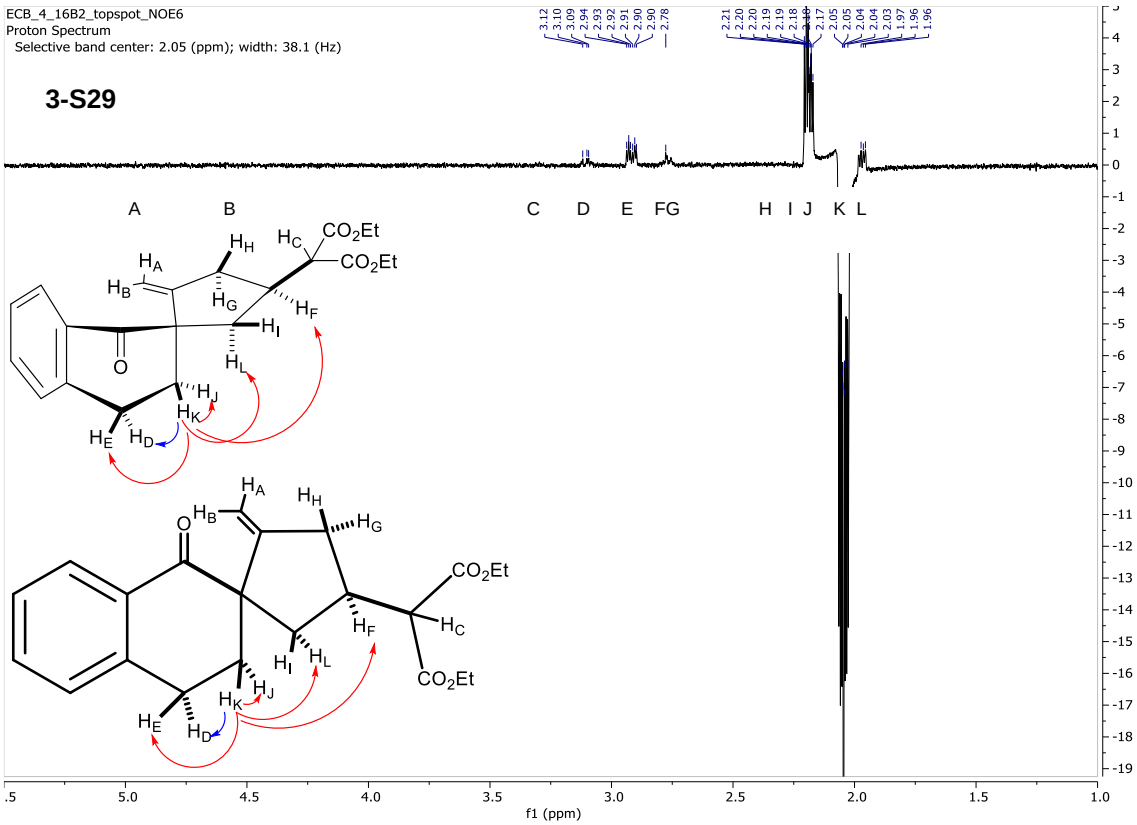

ECB_4_16B2_topspot_NOE1
Proton Spectrum
Selective band center: 3.32 (ppm); width: 23.5 (Hz)
3.33
2.35
2.34
2.27
2.25
2.24
A B C D E FG H I J K L
3-S29
f1 (ppm)

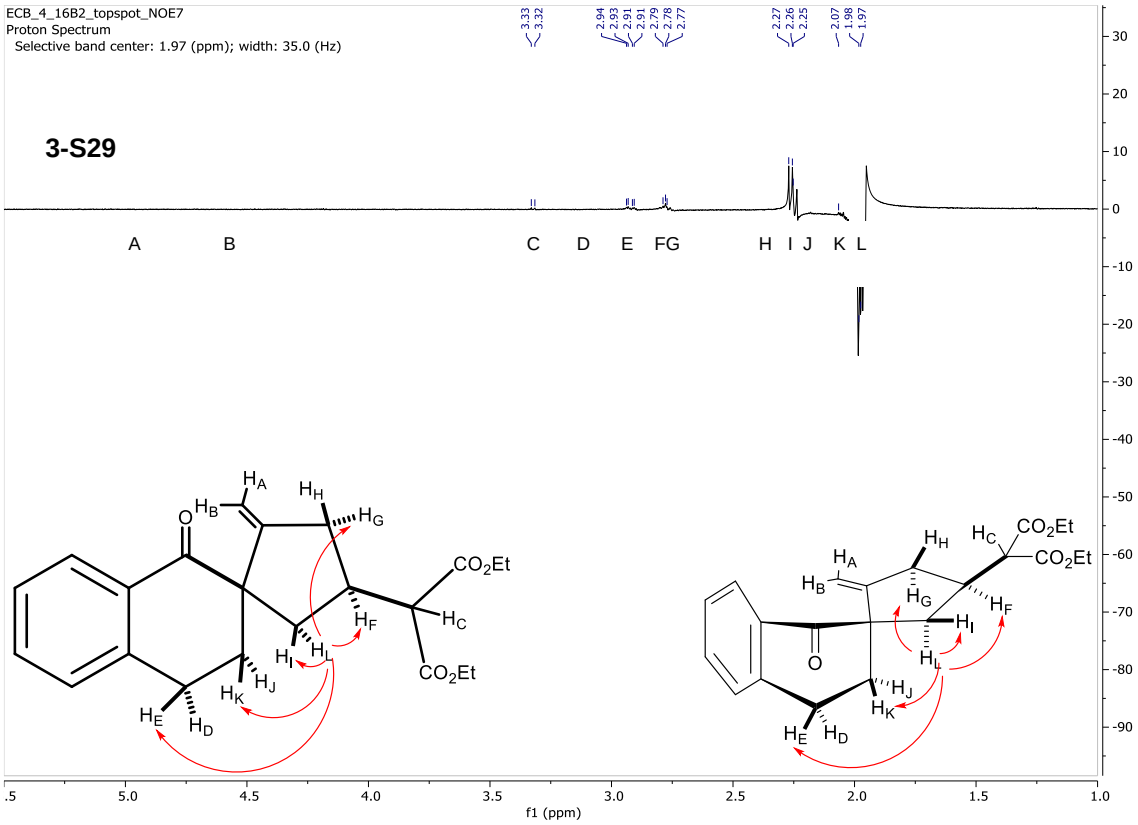

ECB_4_16B2_topspot_NOE2
Proton Spectrum
Selective band center: 3.10 (ppm); width: 48.8 (Hz)
4.59
4.58
4.58
3.10
2.93
2.91
2.90
2.90
2.21
2.20
2.19
2.19
2.18
2.17
2.05
2.04
A B C D E FG H I J K L
3-S29
f1 (ppm)

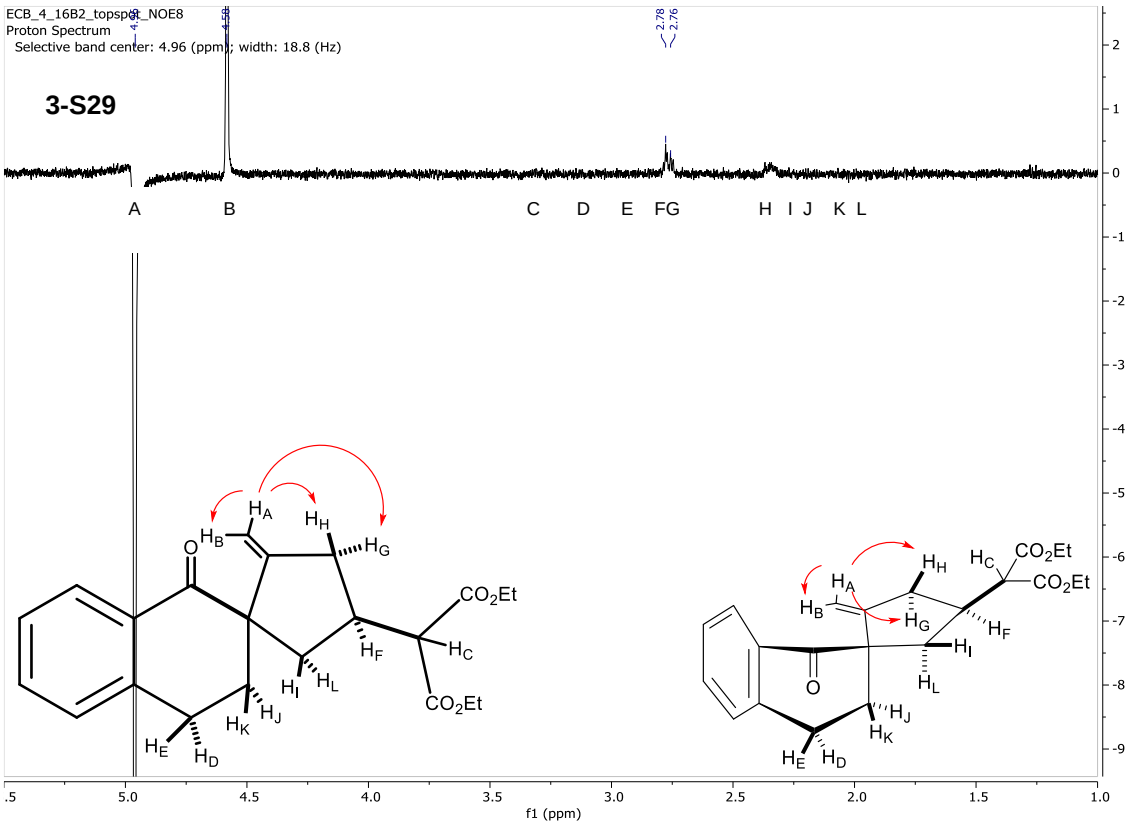

ECB_4_16B2_topspot_NOE3
Proton Spectrum
Selective band center: 2.92 (ppm); width: 42.5 (Hz)
A B C D E FG H I J K L
3-S29
f1 (ppm)

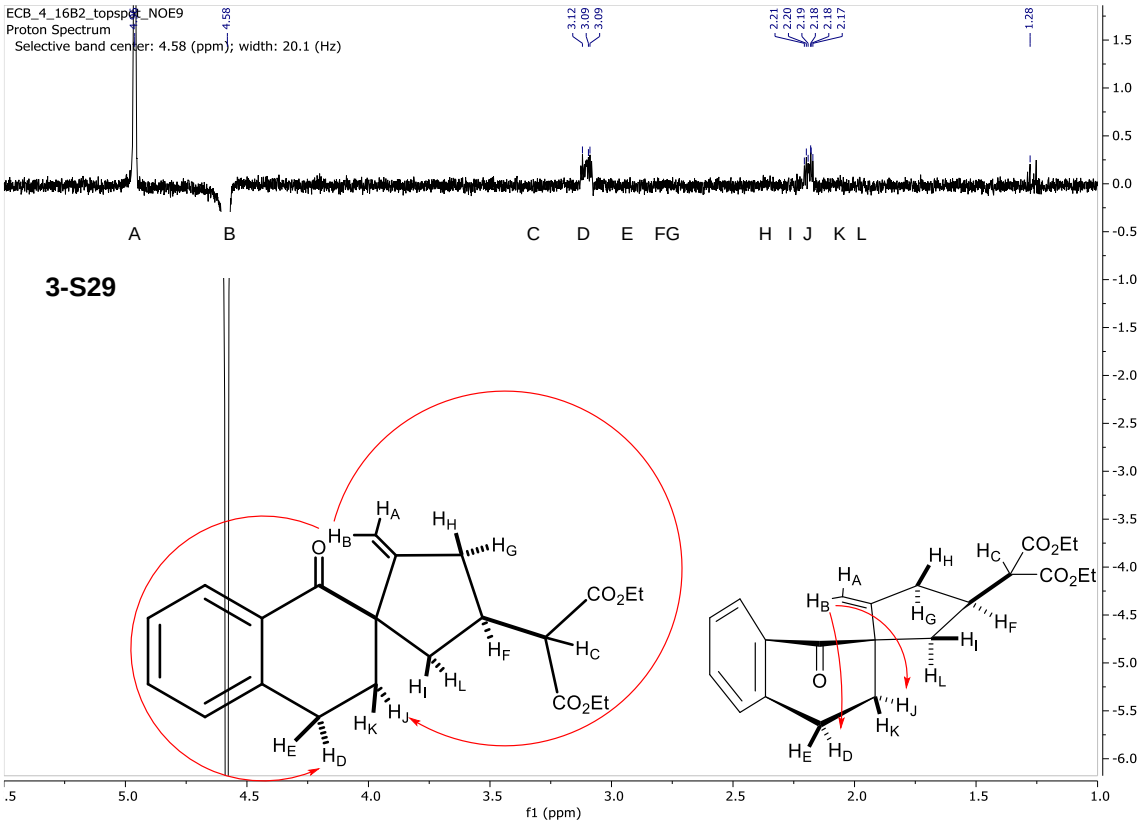

ECB_4_16B2_topspot_NOE4
Proton Spectrum
Selective band center: 2.35 (ppm); width: 50.9 (Hz)
A B C D E FG H I J K L
3-S29
f1 (ppm)

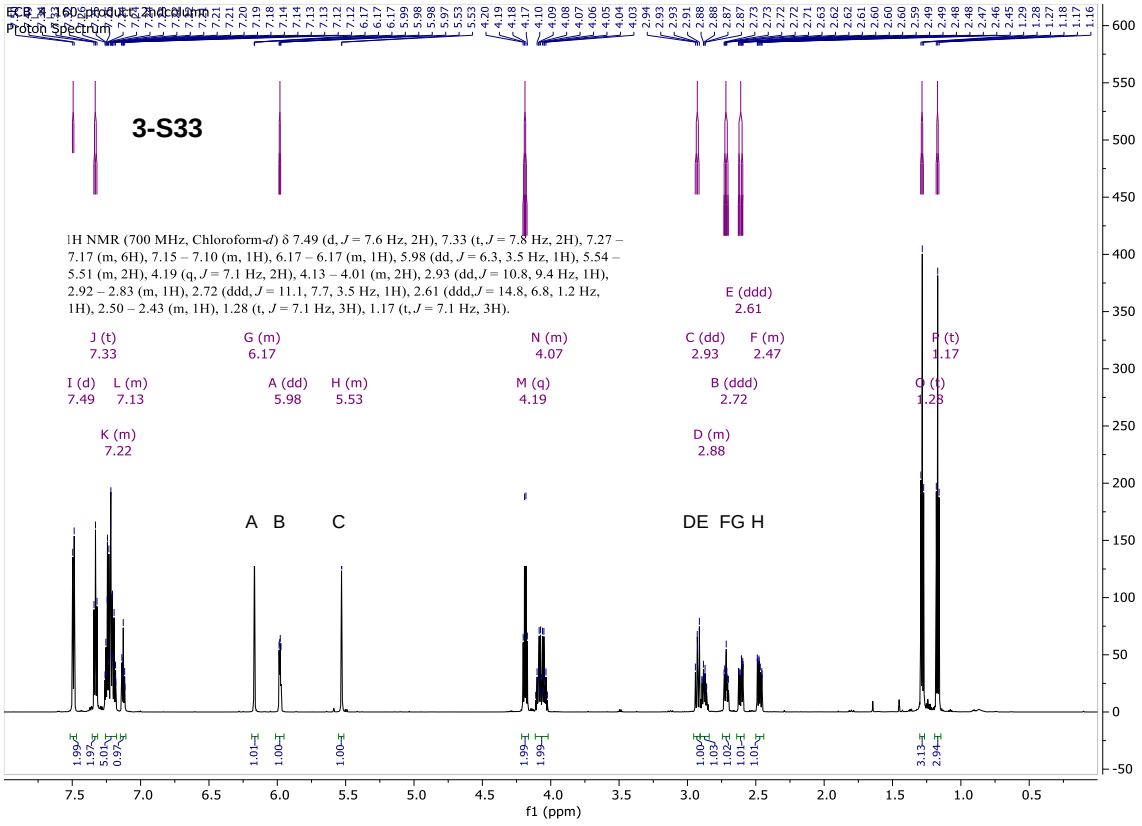

ECB_4_16B2_topspot_NOE5
Proton Spectrum
Selective band center: 2.25 (ppm); width: 40.4 (Hz)
3-S29
A B C D E FG H I J K L
f1 (ppm)

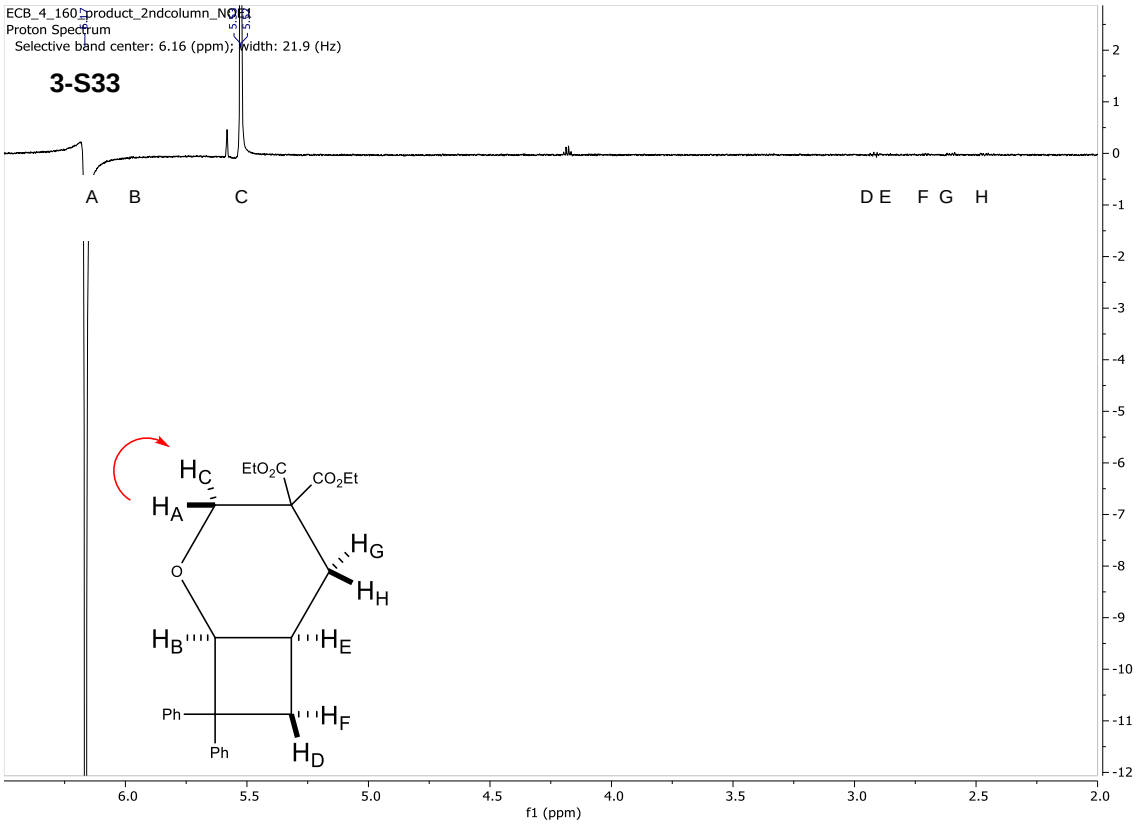

ECB_4_16B2_topspot_NOE6
Proton Spectrum
Selective band center: 2.05 (ppm); width: 38.1 (Hz)
3-S29
A B C D E FG H I J K L
f1 (ppm)

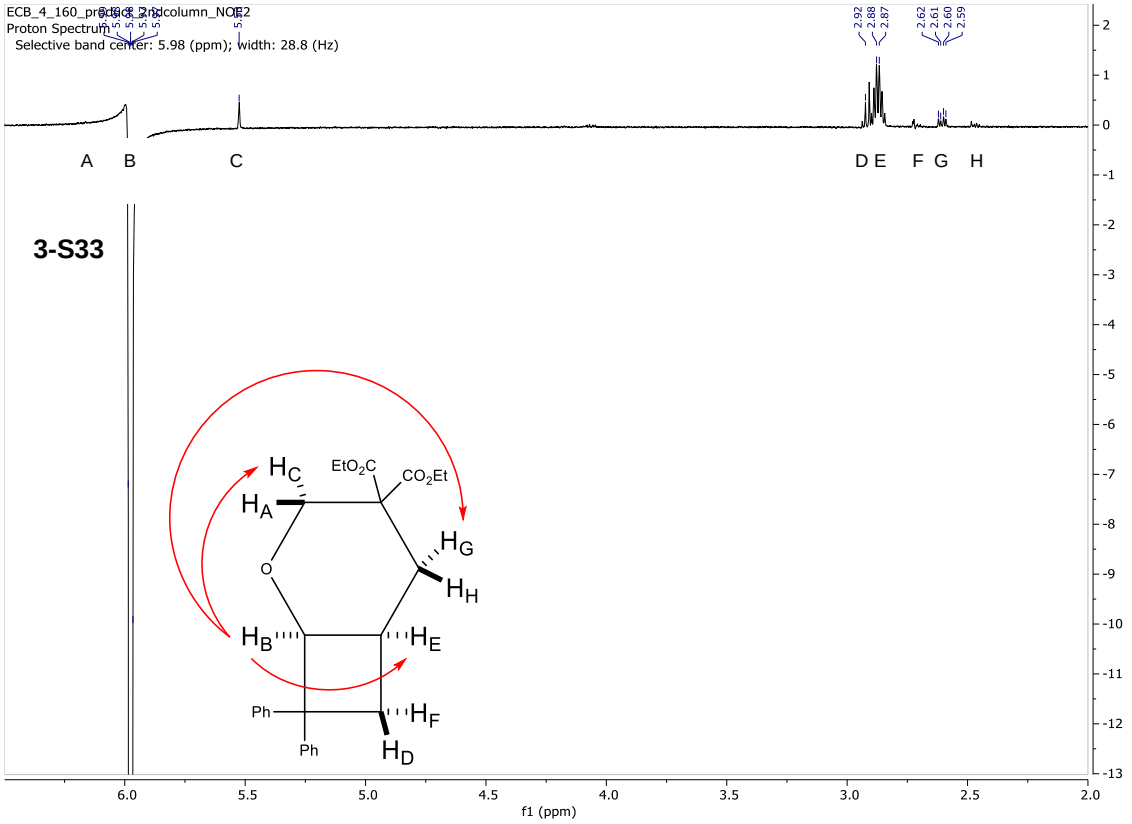

ECB_4_16B2_topspot_NOE7
Proton Spectrum
Selective band center: 1.97 (ppm); width: 35.0 (Hz)
3-S29
A B C D E FG H I J K L
f1 (ppm)

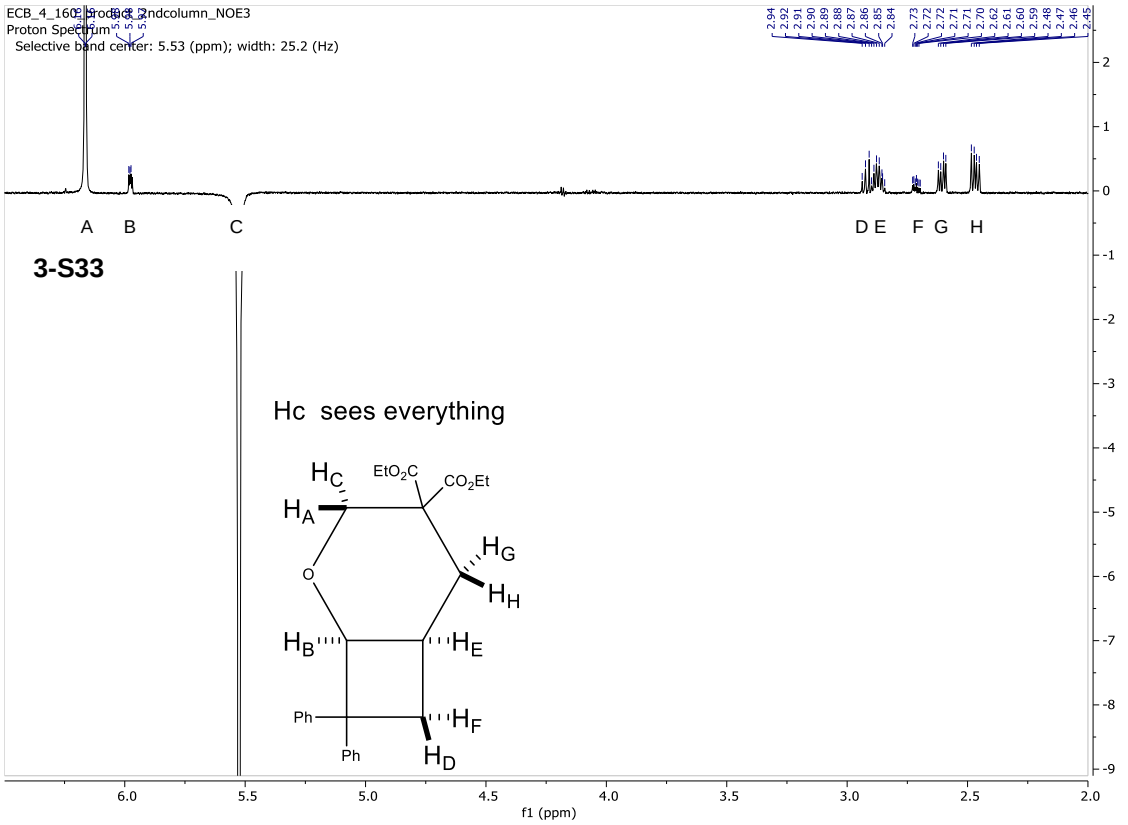

ECB_4_16B2_topspot_NOE8
Proton Spectrum
Selective band center: 4.96 (ppm); width: 18.8 (Hz)
3-S29
A B C D E FG H I J K L
f1 (ppm)

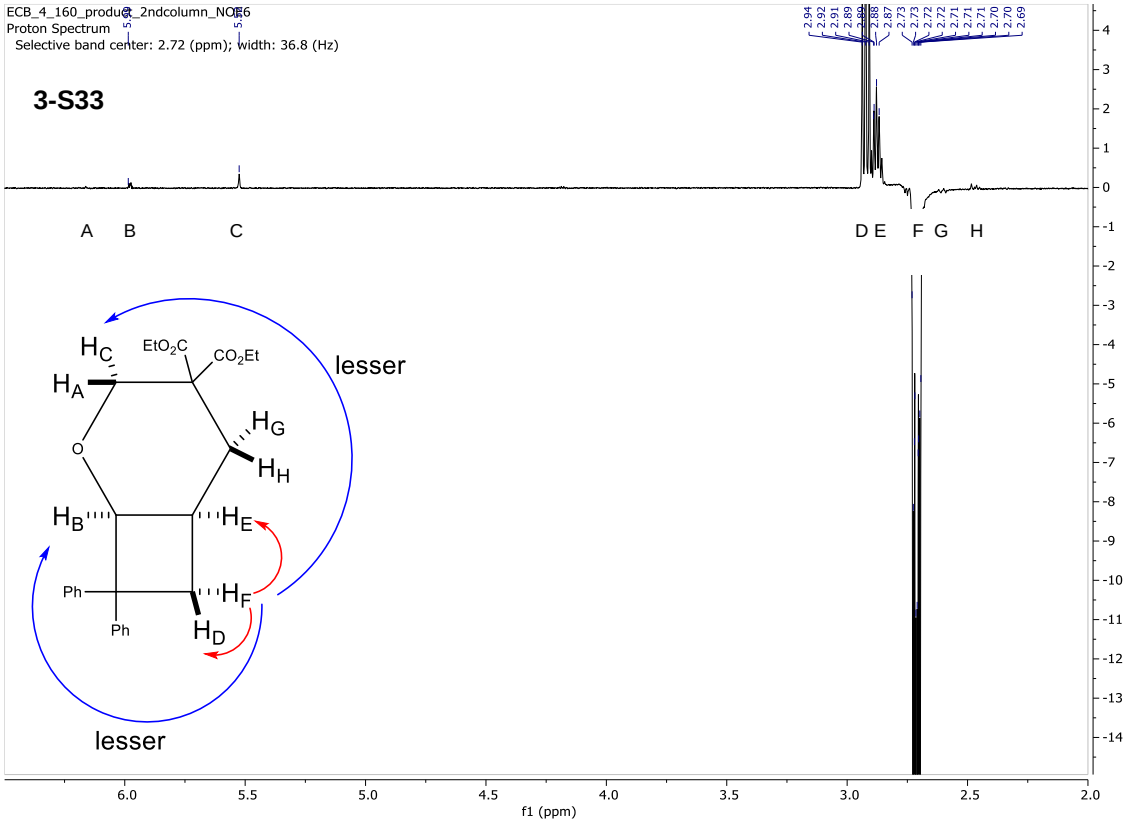

ECB_4_16B2_topspin_NOE9
Proton Spectrum
Selective band center: 4.58 (ppm); width: 20.1 (Hz)
A B C D E FG H I J K L
3-S29
f1 (ppm)

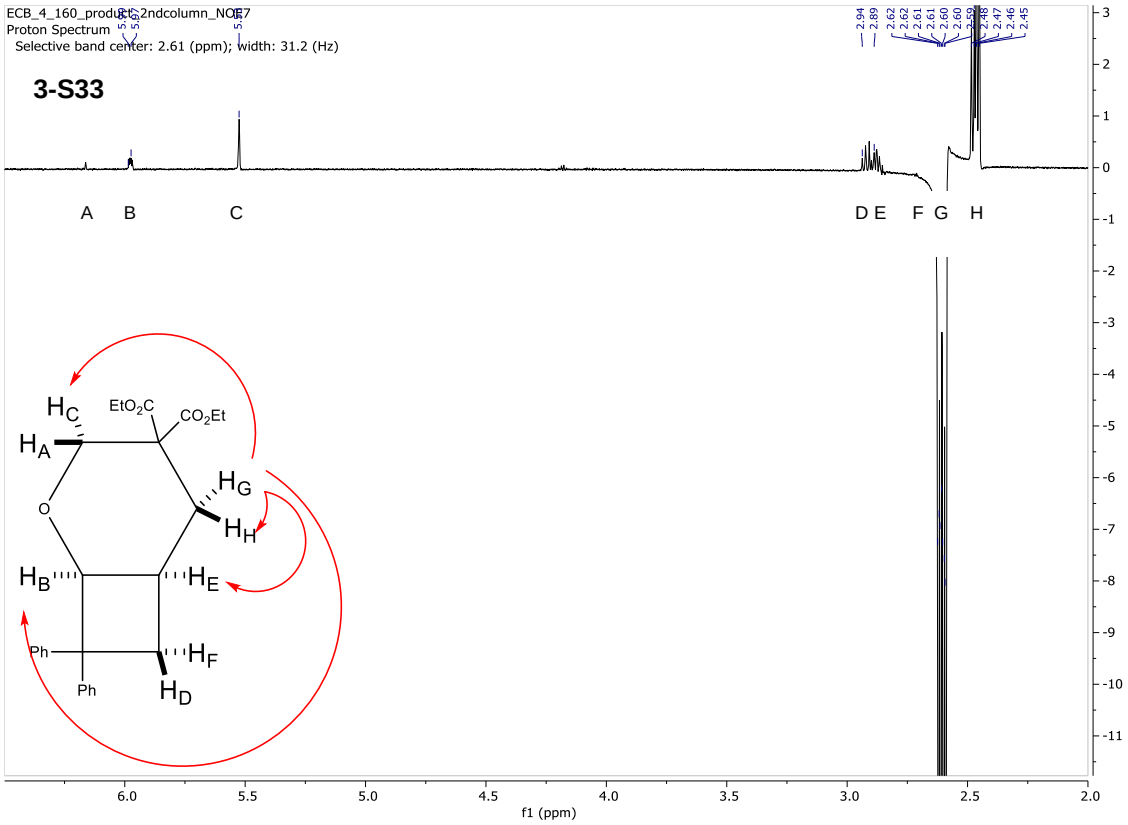

Proton Spectrum
3-S33
A B C DE FG H
f1 (ppm)

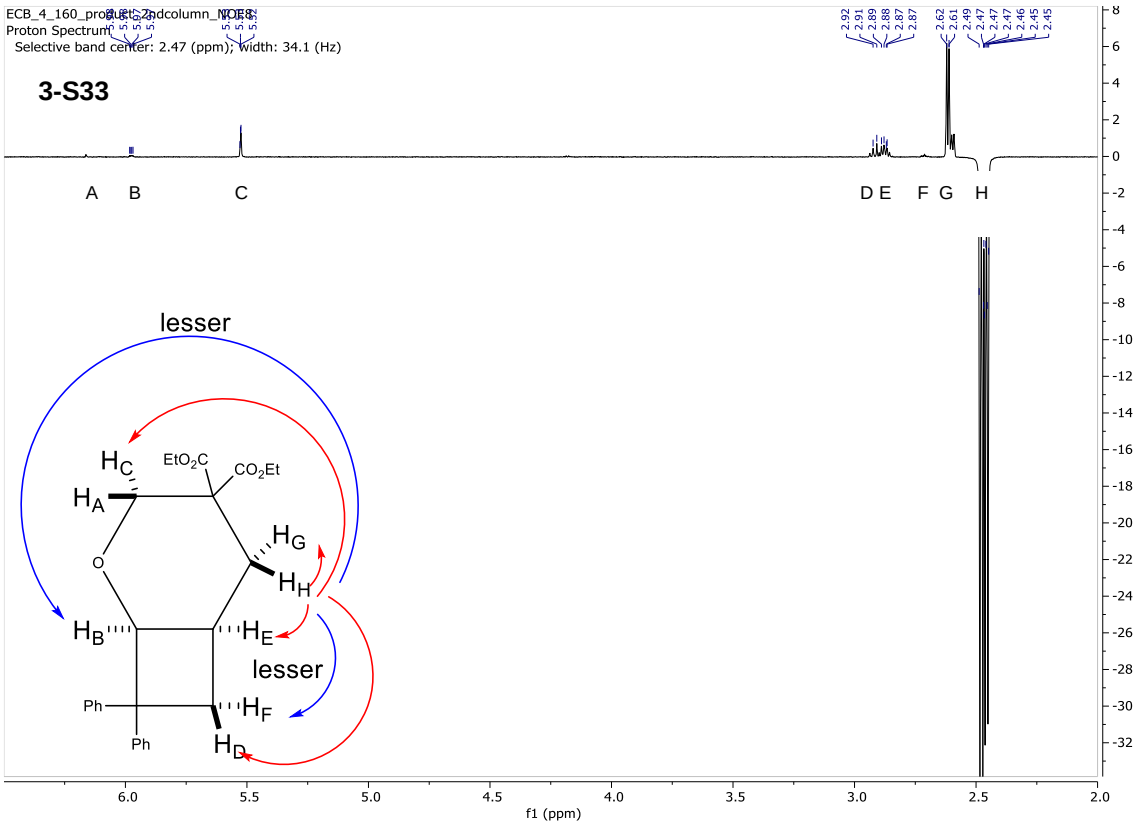

ECB_4_160_product_2ndcolumn_NOE1
Proton Spectrum
Selective band center: 6.16 (ppm); Width: 21.9 (Hz)
3-S33
A B C D E F G H
f1 (ppm)

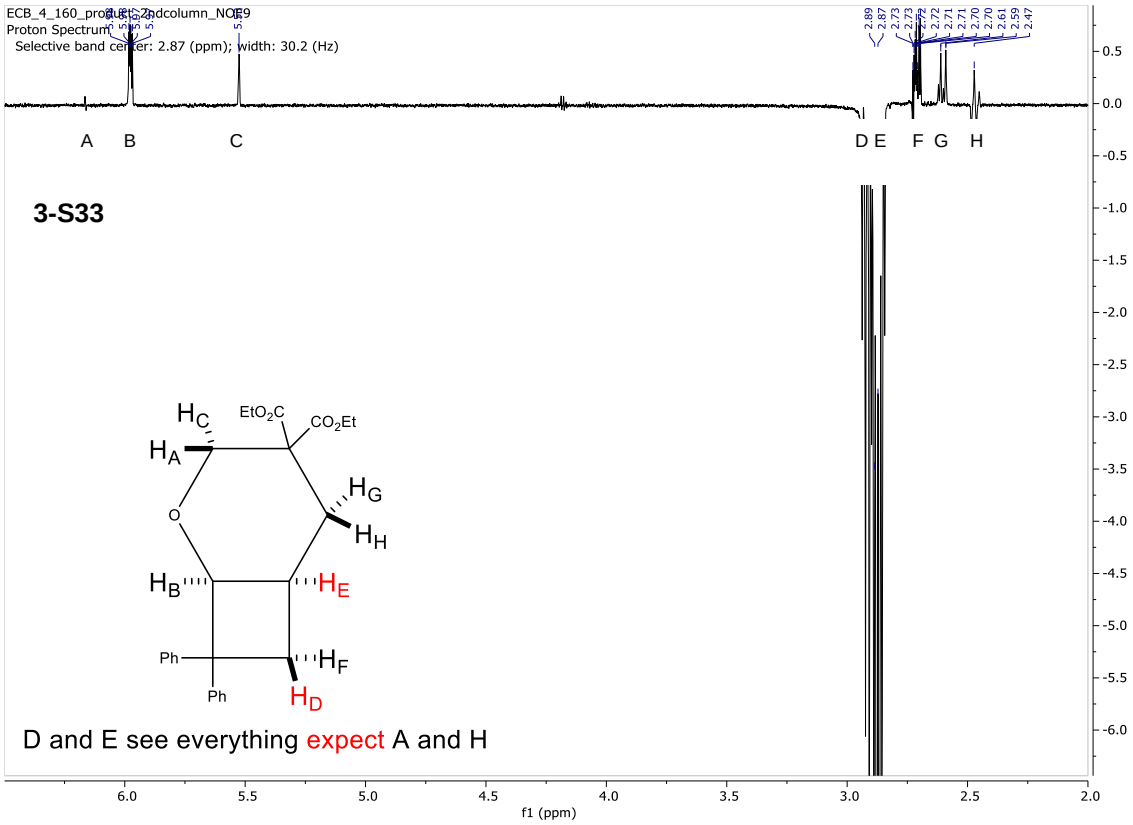

ECB_4_160_product_2ndcolumn_NOE2
Proton Spectrum
Selective band center: 5.98 (ppm); Width: 28.8 (Hz)
3-S33
A B C D E F G H
f1 (ppm)

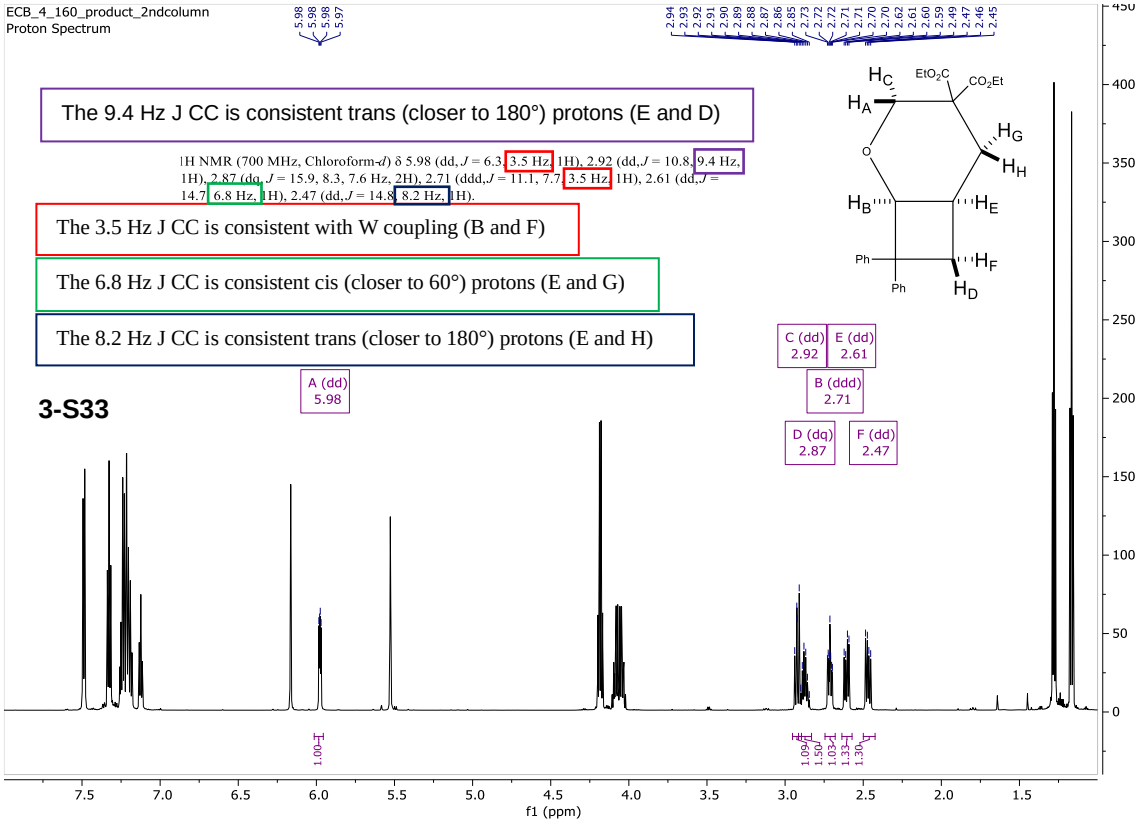

ECB_4_160_product_2ndcolumn_NOE3
Proton Spectrum
Selective band center: 5.53 (ppm); width: 25.2 (Hz)
A B C D E F G H
3-S33
Hc sees everything
f1 (ppm)

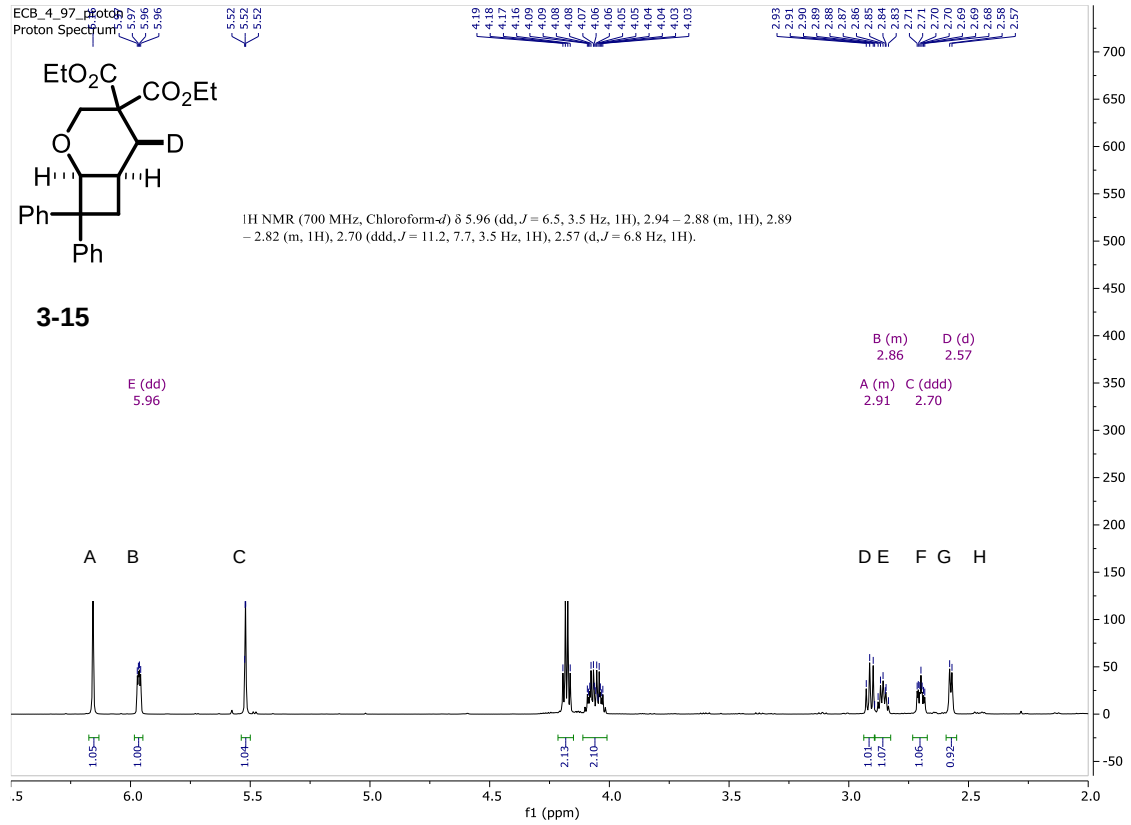

ECB_4_160_product_2ndcolumn_NOE6
Proton Spectrum
Selective band center: 2.72 (ppm); width: 36.8 (Hz)
3-S33
A B C D E F G H
lesser
lesser
f1 (ppm)

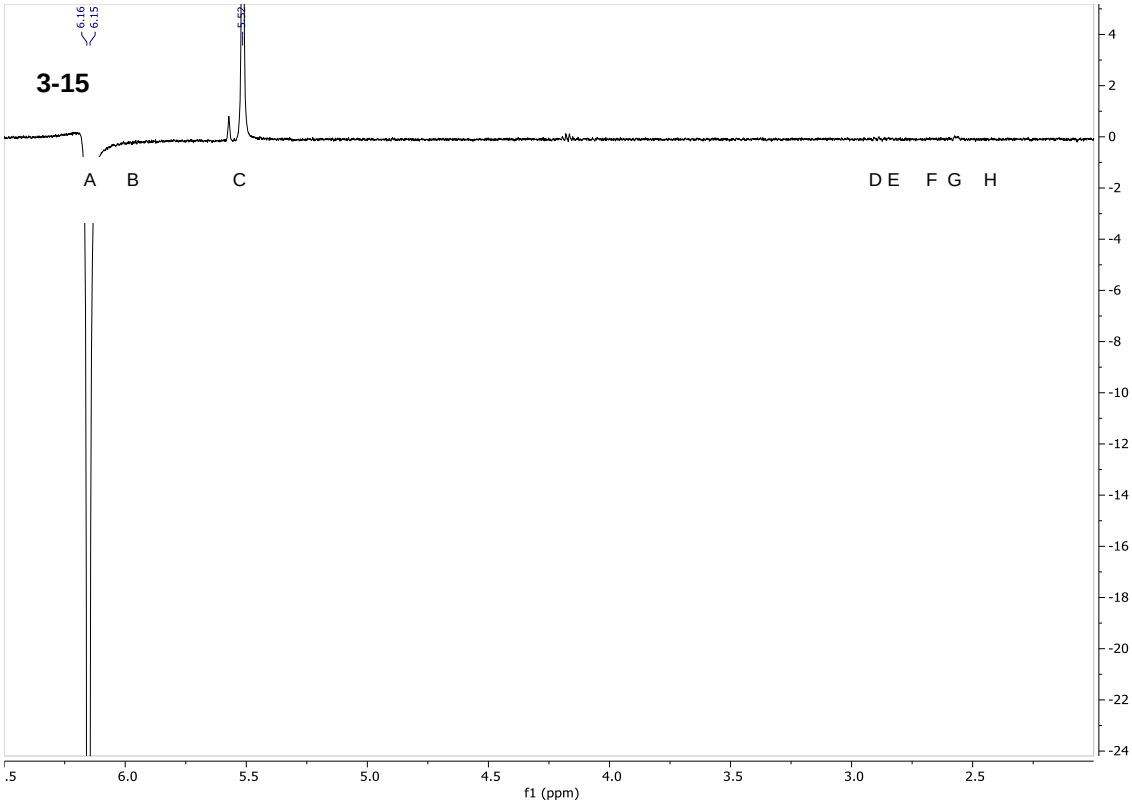

ECB_4_160_product_2ndcolumn_NOE7
Proton Spectrum
Selective band center: 2.61 (ppm); width: 31.2 (Hz)
3-S33
A B C D E F G H
f1 (ppm)


ECB_4_160_product_2ndcolumn_NOE8
Proton Spectrum
Selective band center: 2.47 (ppm); width: 34.1 (Hz)
3-S33
A B C D E F G H
lesser
lesser
f1 (ppm)

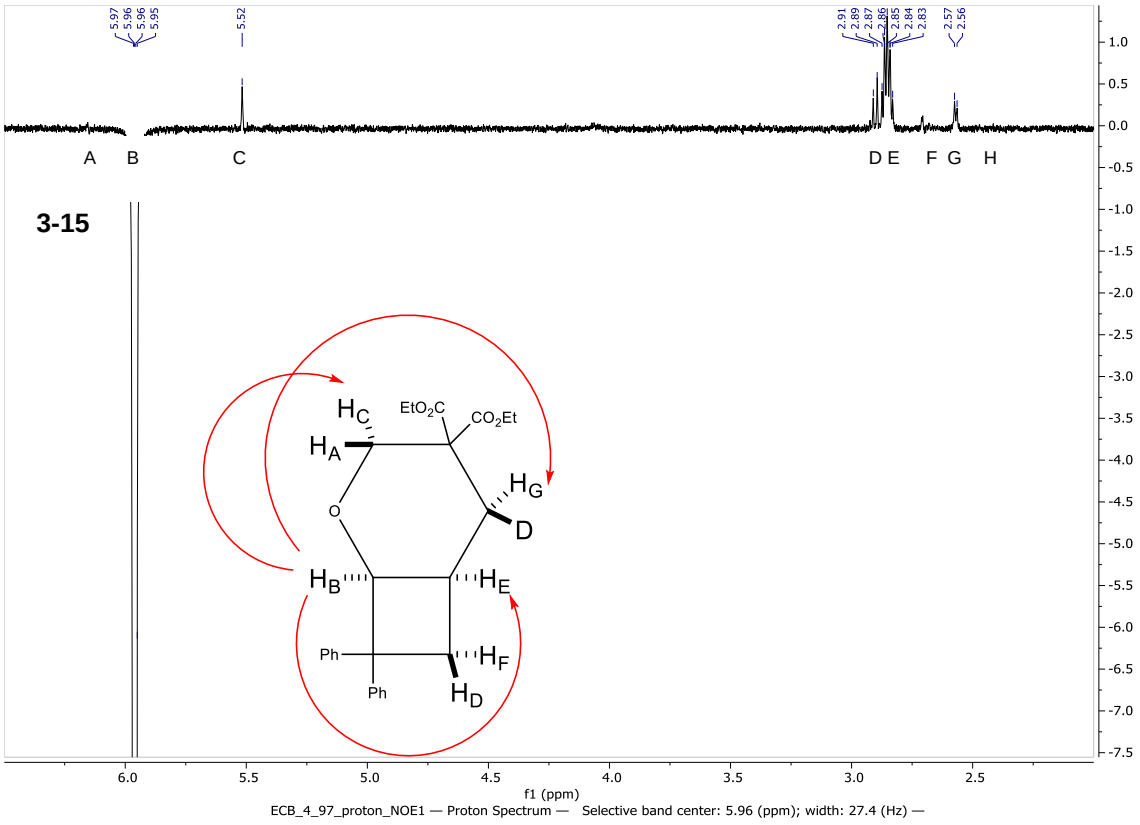

ECB_4_160_product_2ndcolumn_NOE9
Proton Spectrum
Selective band center: 2.87 (ppm); width: 30.2 (Hz)
A B C D E F G H
3-S33
HC EtO2C CO2Et
HA HG
O HH
HB HE
Ph HF
Ph HD
D and E see everything expect A and H
f1 (ppm)


ECB_4_160_product_2ndcolumn
Proton Spectrum
The 9.4 Hz J CC is consistent trans (closer to 180°) protons (E and D)
1H NMR (700 MHz, Chloroform-d) δ 5.98 (dd, J = 6.3, 3.5 Hz, 1H), 2.92 (dd, J = 10.8, 9.4 Hz, 1H), 2.87 (dq, J = 15.9, 8.3, 7.6 Hz, 2H), 2.71 (ddd, J = 11.1, 7.7, 3.5 Hz, 1H), 2.61 (dd, J = 14.7, 6.8 Hz, 1H), 2.47 (dd, J = 14.8, 8.2 Hz, 1H).
The 3.5 Hz J CC is consistent with W coupling (B and F)
The 6.8 Hz J CC is consistent cis (closer to 60°) protons (E and G)
The 8.2 Hz J CC is consistent trans (closer to 180°) protons (E and H)
A (dd) 5.98
C (dd) 2.92
E (dd) 2.61
B (ddd) 2.71
D (dq) 2.87
F (dd) 2.47
3-S33
f1 (ppm)

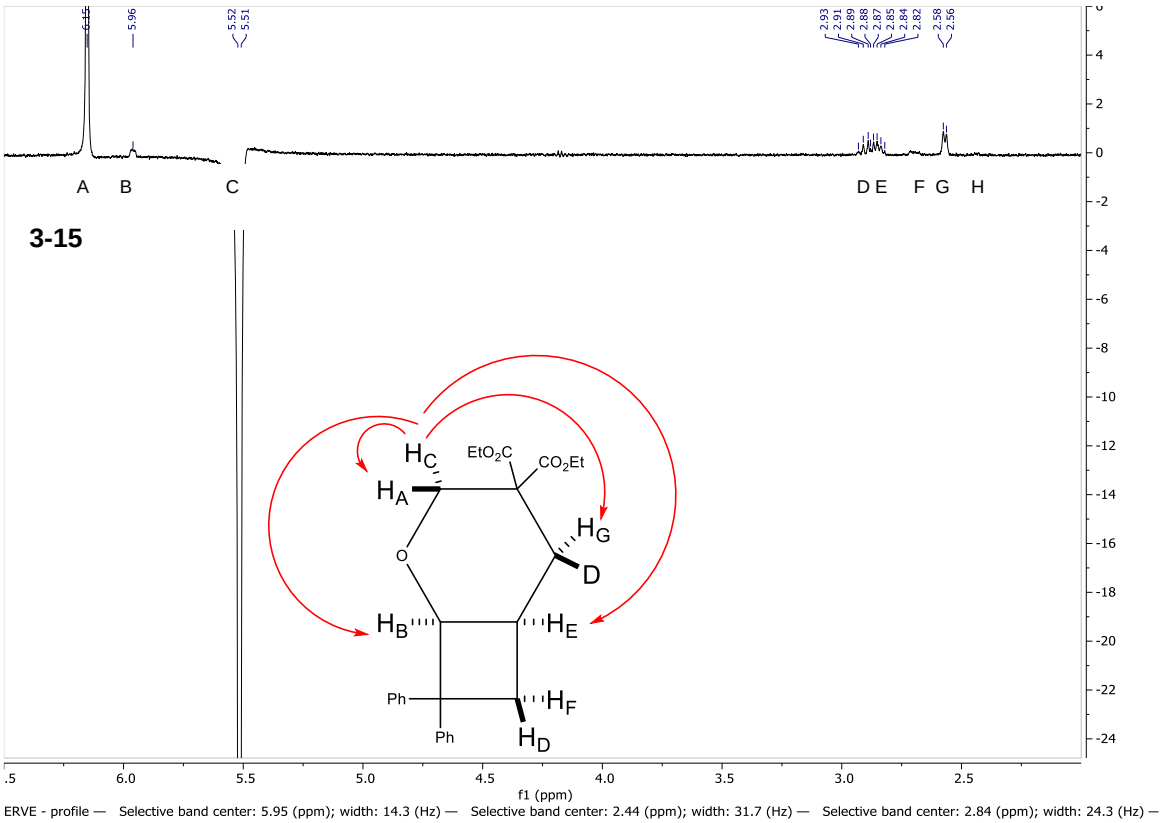




ERVE - profile — Selective band center: 5.95 (ppm); width: 14.3 (Hz) — Selective band center: 2.44 (ppm); width: 31.7 (Hz) — Selective band center: 2.84 (ppm); width: 24.3 (Hz) —



ECB_4_97_proton_NOE1 — Proton Spectrum — Selective band center: 5.96 (ppm); width: 27.4 (Hz) —



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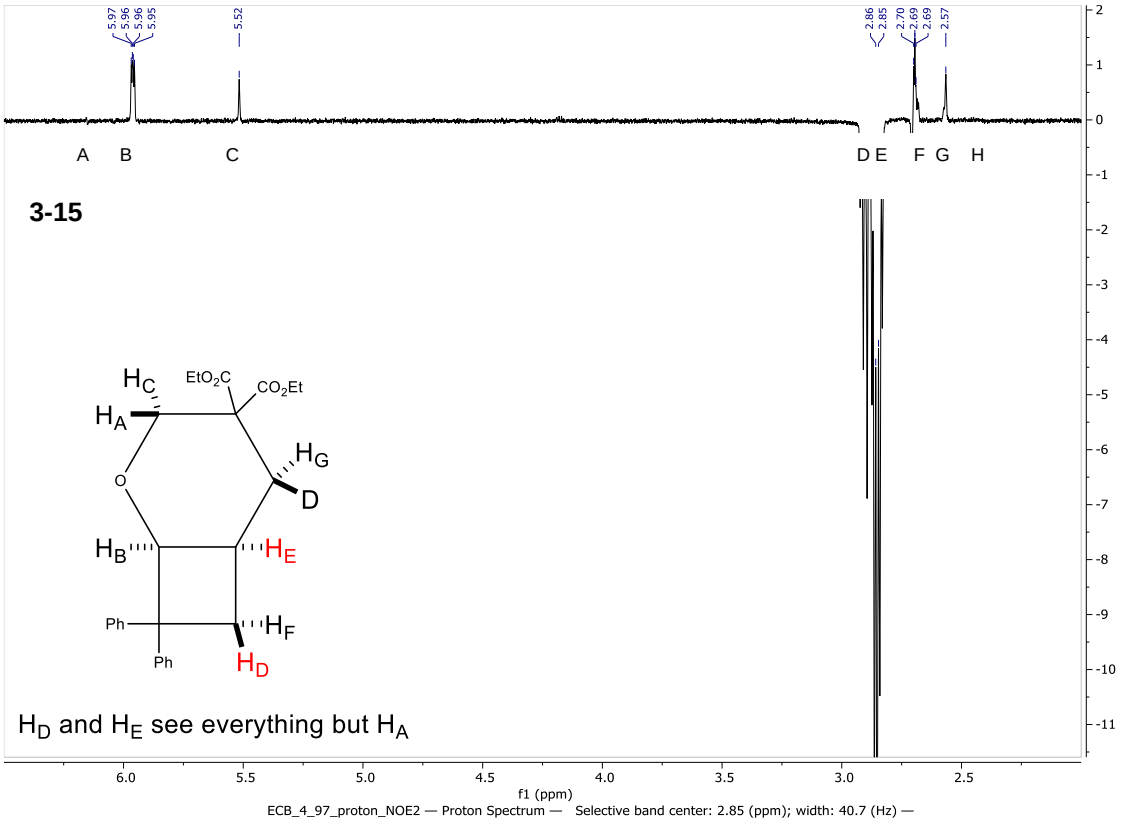
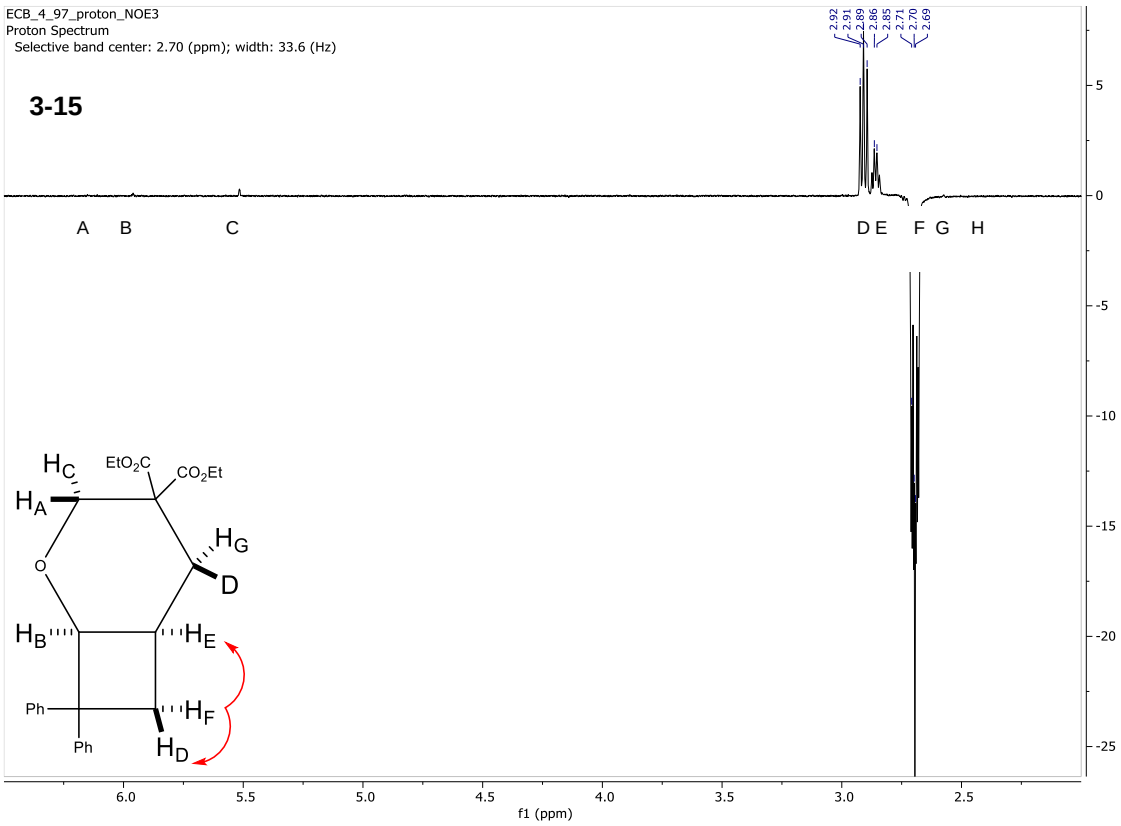

5.97
5.96
5.96
5.95
5.52
2.86
2.85
2.70
2.69
2.69
2.57
A B C D E F G H
3-15
HC
EtO2C
CO2Et
HA
HG
O
D
HB
HE
Ph
HF
Ph
HD
HD and HE see everything but HA
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)
ECB_4_97_proton_NOE2 — Proton Spectrum — Selective band center: 2.85 (ppm); width: 40.7 (Hz) —


ECB_4_97_proton_NOE3
Proton Spectrum
Selective band center: 2.70 (ppm); width: 33.6 (Hz)
2.92
2.91
2.89
2.86
2.85
2.71
2.70
2.69
3-15
A B C D E F G H
HC
EtO2C
CO2Et
HA
HG
O
D
HB
HE
Ph
HF
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HD
6.0
5.5
5.0
4.5
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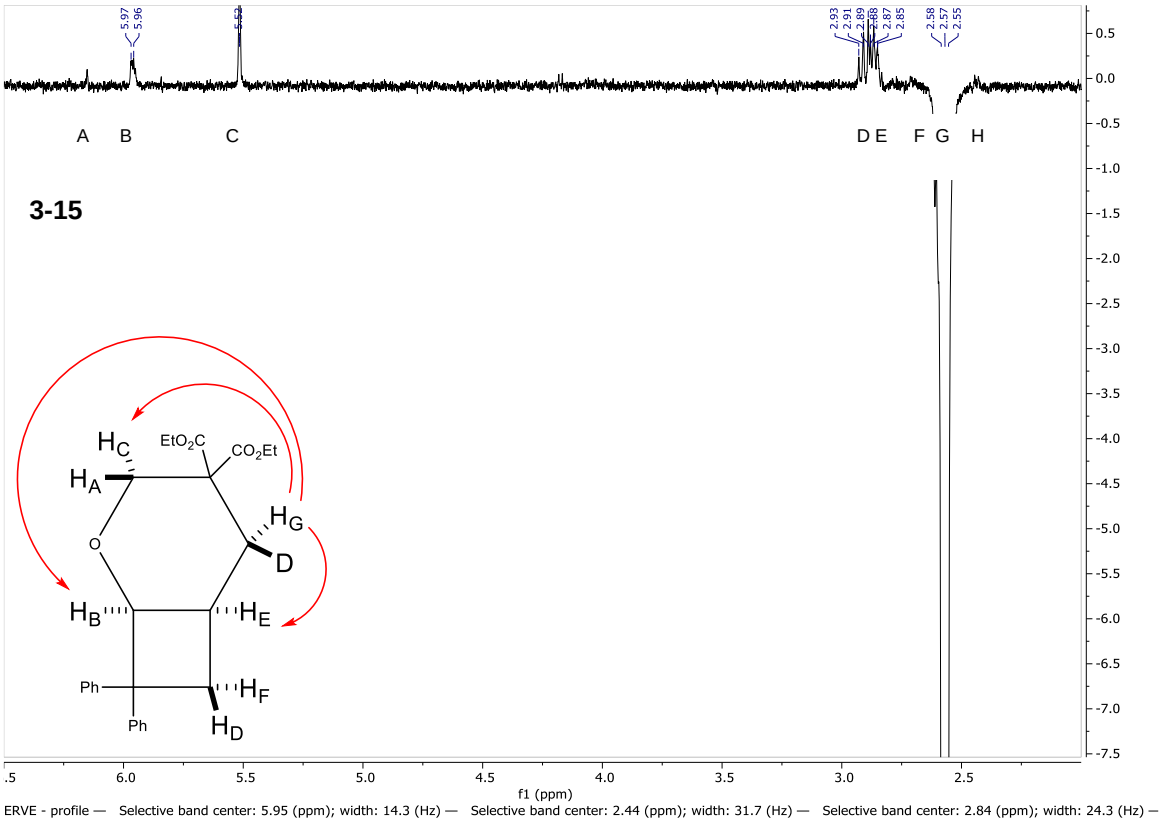
3.5
3.0
2.5
f1 (ppm)



ERVE - profile — Selective band center: 5.95 (ppm); width: 14.3 (Hz) — Selective band center: 2.44 (ppm); width: 31.7 (Hz) — Selective band center: 2.84 (ppm); width: 24.3 (Hz) —

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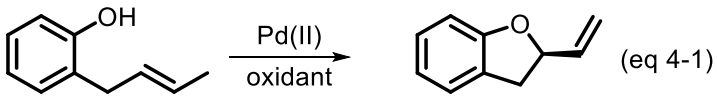
Chapter 4

Preliminary Results of Palladium-Catalyzed Alkene Difunctionalization Reactions

4.1 Introduction to Dihydrobenzofurans

Dihydrobenzofurans and benzofurans are prominent structures in natural products exhibiting biological activity.[1] Transition metal induced cyclizations of *o*-allyl phenols for the synthesis of dihydrobenzofurans has been known since 1976. Hosokawa and co-workers demonstrated the oxidative cyclization of **4-1** to **4-2** via palladium(II) (eq 4-1).[2] Since then, there has been substantial interest in the cyclizations of phenols to yield

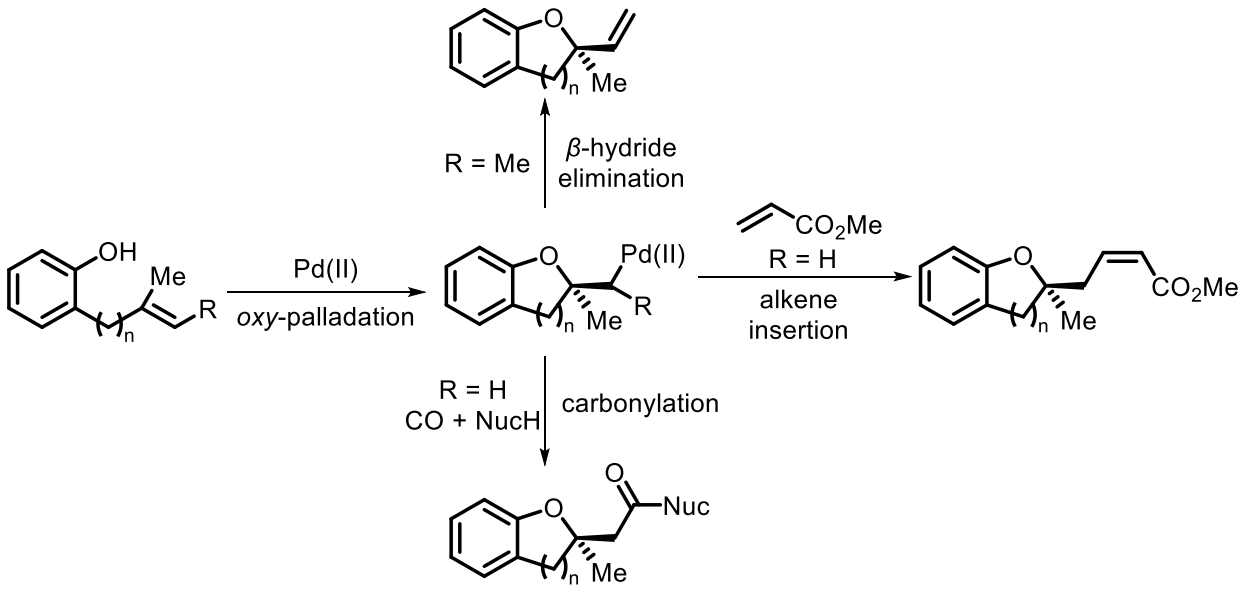
Hosokawa 1976 [2]



4-1 **4-2**

dihydrobenzofuran products.[3] In general, the most common approach has been a transition metal-catalyzed strategy. A shown in **Scheme 4-1**, several different

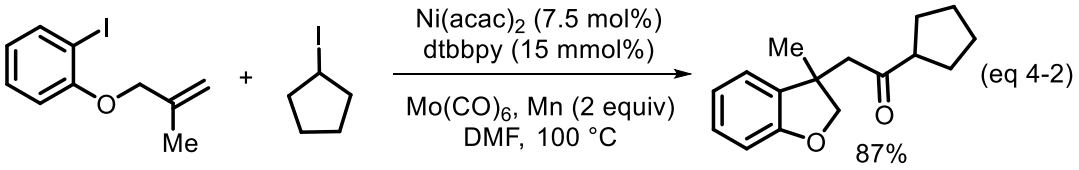
Scheme 4-1: Tietze and co-workers' cyclizations of allylic phenols



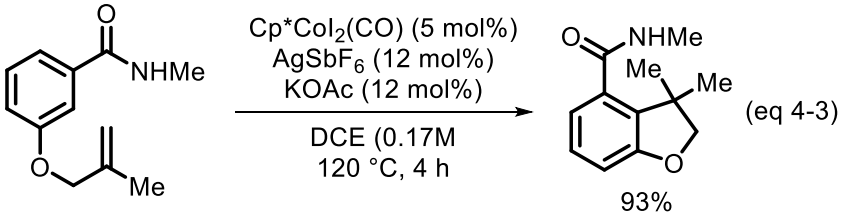
functionalization possibilities exist after the first oxy-palladation step. Similar to Hosokawa, following *oxy*-palladation, the palladium(II) intermediate may undergo beta-hydride elimination. Tietze and co-workers reported the Pd-alkyl intermediate after *oxy*-palladation being trapped by carbon monoxide or methyl acrylate; however, they biased the system by eliminating the possibility of beta-hydride elimination as to allow for nucleophilic capture or alkene insertion.[4]

Another common strategy used to target dihydrobenzofurans via a transition metal-catalytic cyclization is to utilize allylic phenyl ethers. In general, these methods involve a key migratory insertion event where the transition metal inserts itself into the coordinating olefin. Geng and co-workers report a nickel-catalyzed cyclization where they capture the Pd-alkyl intermediate arising from migratory insertion with carbon monoxide. A subsequent reductive elimination gives the product seen in eq 4-2.[5] Carral-Menoyo and

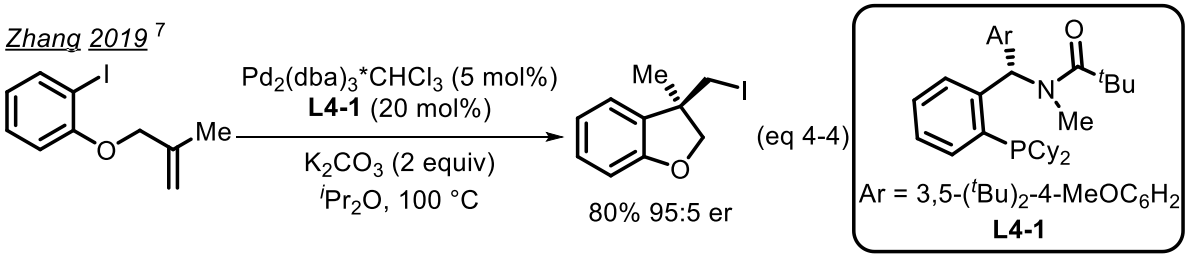
Geng 2021 [5]



Carral-Menoyo 2020 [6]



Zhang 2019 [7]



co-workers report a cobalt-catalyzed cyclization utilizing an amide directing group to facilitate C-H activation. From the Co-aryl intermediate, the migratory insertion into the 1,1 substituted olefin takes place and subsequent protonation of the metal-alkyl intermediate yields the product shown in eq 4-3.[6] Lastly, Zhang and co-workers report an enantioselective Pd-cyclization where the iodine from oxidative addition returns to undergo the reductive elimination and form a new alkyl-halogen bond (eq 4-4). This transformation uses the chiral ligand **L4-1** to impart the desired enantioselectivity through the migratory insertion step.[7]

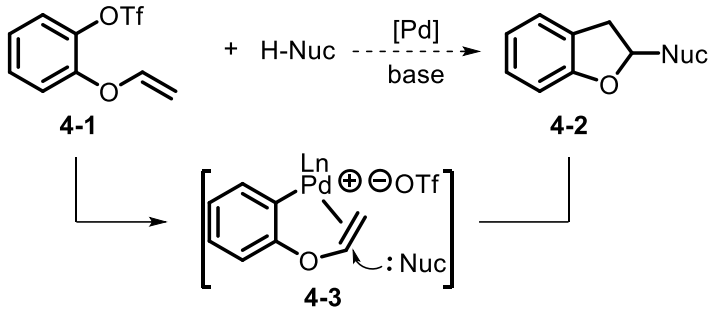
The work described in this chapter is comprised of both the author's (ECB), Alan Wortman's (AW), Chen Lei's (CL), and Jim Shepich III's (JS3) contributions. AW conducted reaction optimization (**Table 4-1**, Entry 2-17). CL conducted reaction optimization (**Table 4-2**) and assembly of preliminary substrate scope (**Scheme 4-4**). JS3 conducted reaction optimization (Table 4-3, Table 4-4) and ran recrystallization purifications (eq 4-10, eq 4-11) We have decided to include AW's, CL's, and JS3's results in this dissertation because they were in close mentorship by the author, and we wished to give the reader the full story about these transformations.

4.2 Preliminary Results for the Construction of Dihydrobenzofurans

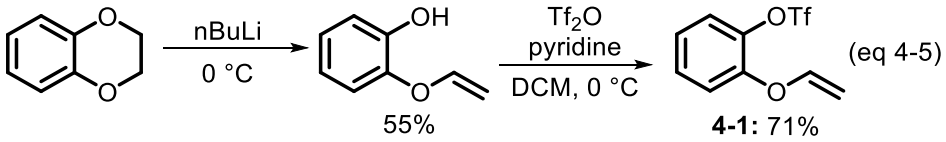
Due to the abundance of dihydrobenzofurans in natural products, we sought to adapt our chemistry to target functionalized dihydrobenzofurans. As shown in **Scheme 4-2** we reasoned we could substitute in a heteroatom (oxygen) for the methylene spacer in our 2-allylphenyl triflate substrate to make a vinyl ether aryl triflate (**4-1**). We hypothesized our vinyl ether could participate in our Pd-catalyzed alkene difunctionalization reactions with exogenous nucleophiles to form functionalized dihydrobenzofurans (**4-2**). Our strategy is fundamentally different than those described previously. Instead of targeting a

key migratory insertion step, our fundamental step would be an attack of the coordinated alkene by an exogenous nucleophile (**4-3**). This new methodology would readily access new functionalizations of dihydrobenzofurans than have been previously reported.

Scheme 4-2: Proposed strategy to target dihydrobenzofurans



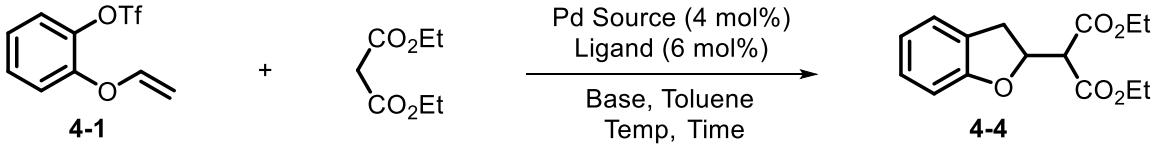
The starting substrate vinyl ether aryl triflate (**4-1**) can be made in two simple steps. As shown in eq 4-5, treating benzo-1,4-dioxane with *n*BuLi gave 55% yield of the ring opened phenol. Subsequent triflation with Tf_2O in DCM (eq 4-6) yielded 71% of our desired starting material.



We set out to optimize the desired reaction. During optimization it was discovered the reaction is air and/or moisture sensitive. Reaction screens conducted in our typical Teflon-coated 4 mL screw cap vials yielded only unreacted starting material regardless of reaction conditions. Once this was known, screens were conducted in Schlenk tubes under a nitrogen atmosphere and the desired product was observed. **Table 4-1** details a selection of our preliminary reaction screens. Entry 1 shows the first successful product formation. With $Pd(OAc)_2$, ligand $P(cy)_3HBF_4$, and LiO^tBu in Toluene, **4-1** was coupled with diethyl malonate to provide **4-4** in 27% isolated yield. Ligand screens (Entry 2-9) proved unfruitful until Brettphos exhibited promising reactivity (Entry 10). A brief screen of palladium pre-catalysts gave similar reactivity to $Pd(OAc)_2$ without showing drastic

improvement (Entry11-13). Switching bases away from LiO^{t}Bu inhibited the desired reactivity (Entry 14-15). Interestingly, reducing the time and temperature of the reaction allowed for similar conversion as Entry 10, however, with the remaining starting material **4-1** present in the crude reaction the potential exists to increase overall isolated yields (Entry 17). Additional reaction conditions have been investigated; however, the conditions were screened outside of Schlenk conditions and such conditions should be revisited.

Table 4-1: Preliminary optimization studies

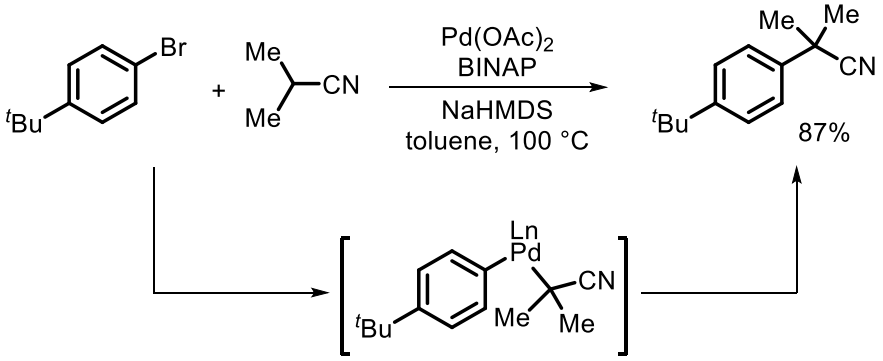


Entry	Pd Source	Ligand	Base	Temp	Time	Result
1	$Pd(OAc)_2$	$P(cy)_3HBF_4$	LiO^{t}Bu	95 °C	15 h	**4-4:** 27% isolated **4-1:** 15% recovered
2	$Pd(OAc)_2$	dppf	LiO^{t}Bu	95 °C	15 h	No Reaction
3	$Pd(OAc)_2$	CPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** Trace
4	$Pd(OAc)_2$	RuPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** Trace
5	$Pd(OAc)_2$	P(*o*-tol)$_3$	LiO^{t}Bu	95 °C	15 h	No Reaction
6	$Pd(OAc)_2$	rac-BINAP	LiO^{t}Bu	95 °C	15 h	No Reaction
7	$Pd(OAc)_2$	N-XantPhos	LiO^{t}Bu	95 °C	15 h	No Reaction
8	$Pd(OAc)_2$	dppe	LiO^{t}Bu	95 °C	15 h	No Reaction
9	$Pd(OAc)_2$	$P(^tBu)_3HBF_4$	LiO^{t}Bu	95 °C	15 h	No Reaction
10	$Pd(OAc)_2$	BrettPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** 36% isolated
11	$Pd(acac)_2$	BrettPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** 36% (NMR)
12	$Pd(TFA)_2$	BrettPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** 21% (NMR)
13	$Pd_2(dba)_3$	BrettPhos	LiO^{t}Bu	95 °C	15 h	**4-4:** 15% (NMR)
14	$Pd(OAc)_2$	BrettPhos	Cs_2CO_3	95 °C	15 h	**4-4:**Trace
15	$Pd(OAc)_2$	BrettPhos	K_3PO_4	95 °C	15 h	No Reaction
16	$Pd(OAc)_2$	BrettPhos	LiO^{t}Bu	60 °C	1 h	**4-4:** 33% (NMR)
17	$Pd(OAc)_2$	BrettPhos	LiO^{t}Bu	95 °C	1 h	**4-4:** 38% (NMR) **4-1:** 17% (NMR)

4.3 Introduction to Palladium-Catalyzed Alkene Difunctionalization Reactions with Exogenous Nitrile Nucleophiles

The use of nitriles as coupling partners in Pd-catalyzed reactions has been demonstrated by several groups.[8] Notably, Hartwig's group reports the α-arylation of nitriles.[8a] Hartwig proposes the mechanism of α-arylation of nitriles to go through an inner sphere mechanism where the nitrile carbanion is bound to the metal before reductive elimination (**Scheme 4-3**).[8b] Following after Hartwig's reports, other groups have used carbanions arising from nitriles in palladium couplings. Notably, in these reports, the nitrile carbanion functions in an analogous inter sphere fashion as described by Hartwig.[8d-f] In these reports, more substituted nitriles are more successful coupling partners.

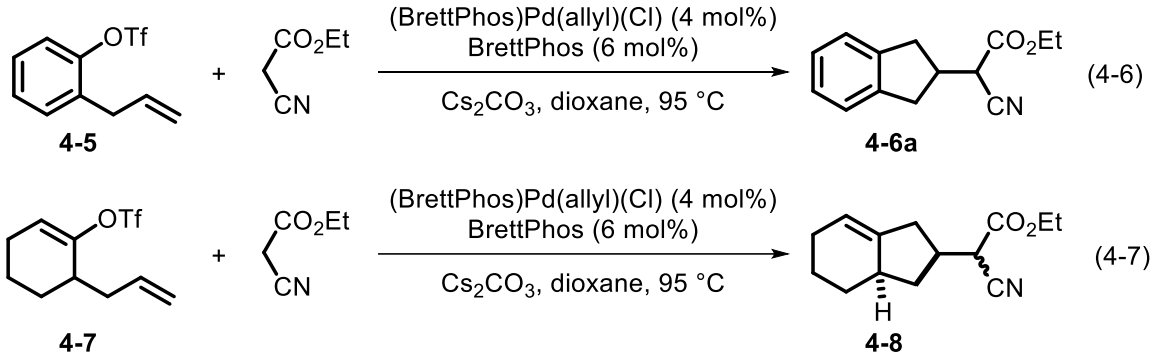
Scheme 4-3: Example of Pd-catalyzed coupling of aryl bromides and nitriles



4.4 Preliminary Results for the Expansion of Nitrile Nucleophiles in Pd-Catalyzed Alkene Difunctionalization Reactions

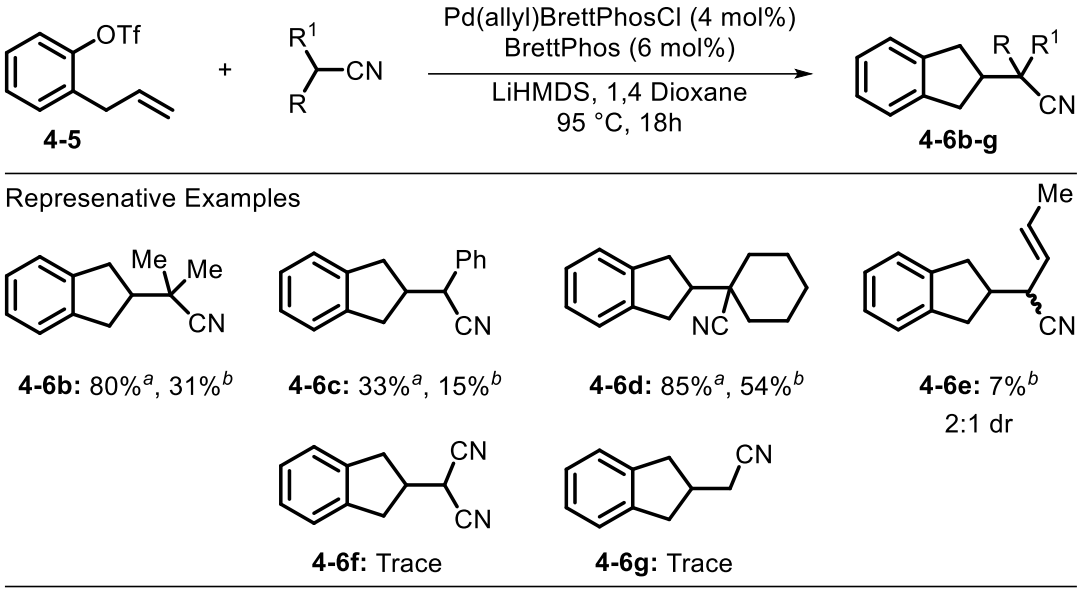
Our group has reported Pd-catalyzed alkene difunctionalization reactions with nitrogen,[9] oxygen,[10] indole,[11] and carbon (enolate)[12] exogenous nucleophiles. In our latest publication, we reported the coupling of aryl and alkenyl triflates with ethyl cyanoacetate (eq 4-6, eq 4-7). Under the standard reaction conditions described in the article the coupling with ethyl cyanoacetate was not observed. Changing the pre-catalyst and base to (BrettPhos)Pd(allyl)(Cl) and Cs_2CO_3 respectively was crucial to obtaining the

desired reactivity. Interestingly, in our case, the nitrile carbanion presumably reacts through an outer sphere attack of the coordinated alkene. With these primary results in hand, we sought to increase the scope of nitriles that participate in our alkene difunctionalization reactions.



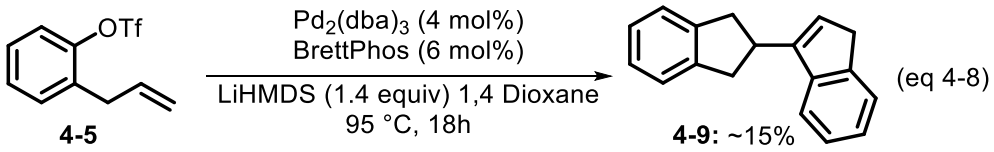
It was quickly determined through rapid screening of reaction conditions that the use of (BrettPhos)Pd(allyl)(Cl) as the precatalyst was essential for any desired reactivity. Once (BrettPhos)Pd(allyl)(Cl) was confirmed as the most effective catalyst, a variety of nitrile nucleophiles were examined as coupling partners with 2-allyl phenol triflate (**Scheme 4-4**). In general, nitriles with higher substitution gave higher yields and worked well as coupling partners. While the crude reaction yield seemed promising, there was difficulty in the isolation of products and the isolated yield suffered. **4-6b** and **4-6d** were isolated in 31% and 54% yield, respectively. The products resulting from less substituted nitriles were isolated in 15% for **4-6c** and 7% for **4-6e**. Product **4-6e** was isolated in a mixture of 2:1 diastereomers. Products **4-6f** and **4-6g** were only observed via NMR in extremely small quantities.

Scheme 4-4: Nitrile nucleophiles coupled with **4-5**



[a]NMR yield with phenanthrene as the internal standard. [b]Isolated yield

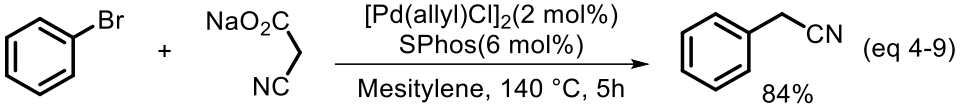
While screening reaction conditions, we observed unique and unexpected reactivity. As shown in (eq 4-8), when running a control experiment with no nucleophile, substrate **4-5** presumably cyclized with itself to give the unexpected carbocycle product **4-9**. The mechanism by which this product is formed is currently unclear. We briefly explored additional reactions with multiple equivalents of aryl triflates and no nucleophile present and observed a variety of cyclization products that were difficult to characterize and isolate. Additional screening and optimization is required to expand on this interesting result.



(eq 4-8)

We still strongly desired to use acetonitrile as a coupling partner due to its simplicity and potential for further functionalization. With our current catalyst conditions failing to couple acetonitrile, we shifted to a decarboxylation strategy. In 2011, Shang and co-workers reported the decarboxylative coupling of cyanoacetate salts with aryl triflates (eq

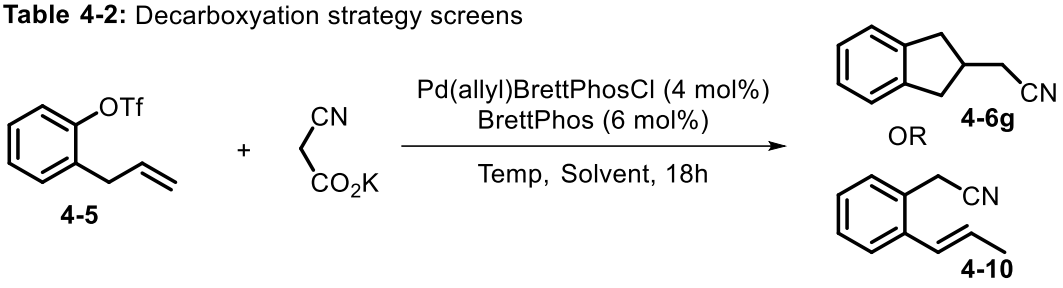
Shang 2011 [13a]



(eq 4-9)

4-9).[13] We hypothesized we could take advantage of the same system for our cyclization. Unfortunately, as seen from select examples in **Table 4-2**, we did not observe any of the desired cyclization (**4-6g**) when utilizing the cyanoacetate potassium salt. We did observe and isolate the direct C-C coupling product with alkene isomerization (**4-10**) in relatively low yields. Additional strategies are needed to fully develop the alkene difunctionalization reactions with aryl and alkenyl triflates and nitrile nucleophiles.

Table 4-2: Decarboxyation strategy screens



Entry	Temp (°C)	Solvent	Conversion	Yield
1	100	1,4 Dioxane	90%	**4-6g:** 0%, **4-10:** trace
2	100	Toluene	90%	**4-6g:** 0%, **4-10:** 10%
3	140	Mesitylene	90%	**4-6g:** 0%, **4-10:** 22%
4	80	1,4 dioxane	30%	**4-6g:** 0%, **4-10:** 0%

4.5 Preliminary Results for Regiodivergent Pd-Catalyzed Alkene Difunctionalization Reactions with Amine Nucleophiles

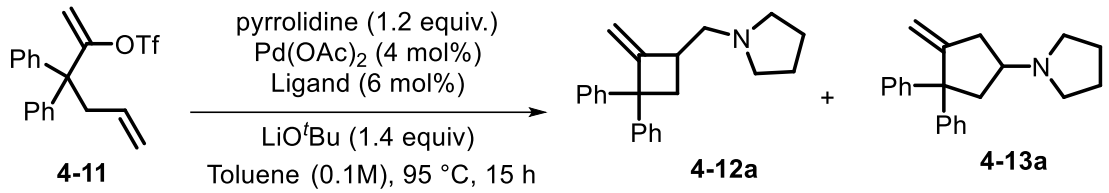
As described in Chapter 3, we have developed a regiodivergent Pd-catalyzed alkene difunctionalization reaction with exogenous malonate nucleophiles for the construction of methylene cyclobutanes. Expanding the scope to nucleophiles other than malonates would greatly increase the overall utility of the reaction. Our group has previously reported successful reactions with exogenous nitrogen and oxygen nucleophiles and we hoped to

leverage this experience to develop a natural extension of the regiodivergent chemistry with nitrogen and/or oxygen nucleophiles.[9-10]

For our initial screens we elected to use substrate **4-11** due to its propensity to yield the cyclobutane product in the previous system and the observation that the cyclobutane product proved harder to select for in general. We began our nucleophilic scope expansion screens with pyrrolidine due to its abundance and success as a nucleophile in our palladium coupling chemistry. We sought to optimize reactions conditions to select for either the cyclobutane product (**4-12a**) or cyclopentane product (**4-13a**) by primarily changing the ligand. **Table 4-3** details selected examples of our ligand screens. After screening over 40 different phosphorus ligands, a general trend was not easily detectable. However, as shown by Entry 1, when no ligand was employed the reaction gives approximately a 1:1 ratio of regioisomers clearly showing the ligand has an effect on the regioselectivity. Three ligands (Entry 4, Entry 9-10) gave selectivity for the methylene cyclobutane isomer and two ligands (Entry 11-12) gave selectivity for the methylene cyclopentane isomer. Entry 4 and Entry 12 gave gratifying results as the ligands gave similar regioselectivity trends with the previous malonate nucleophiles. Interestingly, RuPhos and BrettPhos (Entry 9 and Entry 11) gave opposite selectivities even though they are structurally and electronically similar. Attempts to isolate the mixture of regiomers was met with limited success and significant impurities remained after isolation by column chromatography.

Due to limited success in purification, we sought alternative methods to isolate product **4-12a** and **4-12b**. We envisioned a protonation strategy where the pyrrolidine would be protonated with an organic salt, the resulting solid isolated, and then the organic salt

Table 4-3: Selected ligand screens



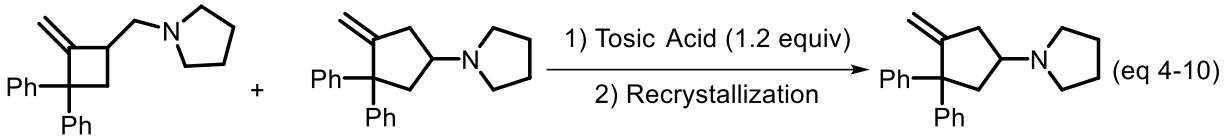
4-11 **4-12a** **4-13a**

Entry	Ligand	Result (%[a], **4-12a** : **4-13a**)
1	none	--, 47:53
2	PMe_3HBF_4	--, 55:45
3	$P(cy)_3HBF_4$	--, 73:27
4	**Tris(2,4-di-^{t}Bu-phenyl)phosphite**	**71%,[a] 76:24**
5	dppe	--, 56:44
6	rac-BINAP	--, 42:58
7	dppf	--, 64:46
8	SPhos	--, 53:47
9	**RuPhos**	**--, 81:19**
10	**$P(^tBu)_3HBF_4$**	**--, 84:16**
11	**BrettPhos**	**48%,[a] 17:83**
12	**dppBz**	**40%,[a] 22:78**

[a]Isolated yields contained varying levels of inseparable impurities

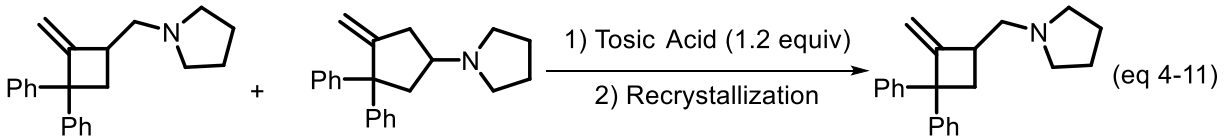
recrystallized to yield the desired products. To this end, we subjected the products isolated from Entry 11 to tosic acid and isolated the resultant organic salt. After a subsequent recrystallization and base wash, we were overjoyed to isolate the pyrrolidine functionalized methylene cyclopentane product **4-13a** cleanly (eq 4-10) in overall 10% yield in 97% regioselectivity. We repeated this method for the mixture of regiomers from Entry 10 and isolated the functionalized methylene cyclobutane product **4-12a** as well (eq 4-11) in overall 20% yield in 97% regioselectivity. The overall yield of these reactions needs improvement; however, the clean isolation of each regioisomer is encouraging. Additional organic acids and recrystallization methods should be screened to obtain

higher overall yields. The recrystallization seems to purify the major isomer for each reaction. It is unclear at this point what the minimum ratio needed separate the regioisomers by recrystallization.



(eq 4-10)

4-12a Entry 11: 17:83 **4-13a** **4-13a:** 10%, 97% regiopure



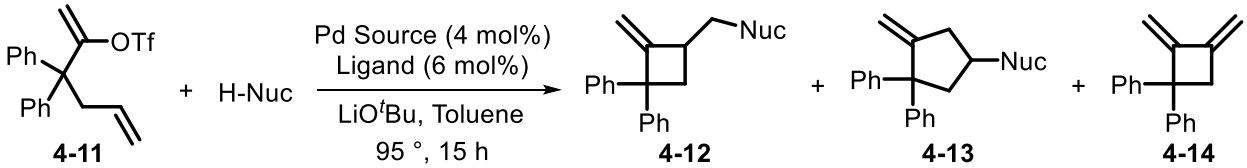
(eq 4-11)

4-12a Entry 10: 84:16 **4-13a** **4-12a:** 20%, 97% regiopure

After we obtained relatively good selectivity of each regioisomer and developed an isolation technique for each regioisomer by recrystallization (**12a** and **13a**), we started to examine the amine scope. We started reaction screens with analogous reaction conditions that achieved high selectivities for the pyrrolidine nucleophile. We started with two ligands that selected highly for the cyclobutane regioisomer **4-12** (RuPhos and $P(^tBu)_3HBF_4$) and two ligands that selected highly for the cyclopentane regioisomer **4-13** (BrettPhos and dppBz). Unfortunately, it quickly became clear additional optimization was required, including potentially another ligand screen. As shown in **Table 4-4** a variety of amines have been screened against our chosen ligands. No desired reaction occurred when aniline was used as the exogenous coupling partner amine (Entry 1-2). Diethylamine did not select for the cyclobutane, but the β-hydride elimination product **4-14** was observed (Entry 3). Diethylamine did show promise in selecting for the cylcopentane isomer, however the NMR yield was low (Entry 4-5). Surprisingly, when employing dppBz as the ligand to select for the 5-membered ring, we observed the formation of the 4-membered ring and **4-14** (Entry 6). Butylamine gave modest selectivity

for each regioisomer (Entry 7-10) and Boc-protected butylamine resulted in decomposition of the starting material (Entry 11-12). Butylamine seemed to have potential for further optimization and switching the base to Cs_2CO_3 gave drastically different results. Changing the palladium source in addition to the base gave increased regioselectivities and NMR yields. Additional optimization is required to fully expand the nitrogen nucleophile scope of this reaction.

Table 4-4: Selected amine nucleophile screens



Entry	Pd Source	H-Nuc (equiv)	Ligand	LiO^{t}Bu equiv	Result (%,[a] **4-12**:**4-13**:**4-14**)
1	$Pd(OAc)_2$	Aniline (1.2)	$P(^tBu)_3HBF_4$	1.4	20%, 0:0:100
2	$Pd(OAc)_2$	Aniline (1.2)	BrettPhos	1.4	Decomposition
3	$Pd(OAc)_2$	Diethylamine (1.2)	$P(^tBu)_3HBF_4$	1.4	30%, 0:0:100
4	$Pd(OAc)_2$	Diethylamine (1.2)	BrettPhos	1.4	13%, 23:77:0
5	$Pd(OAc)_2$	Diethylamine (5)	BrettPhos	5	16%, 18:62:20
6	$Pd(OAc)_2$	Diethylamine (5)	dppBz	5	29%, 76:0:24
7	$Pd(OAc)_2$	Butylamine (5)	RuPhos	5	--, 69:31:00
8	$Pd(OAc)_2$	Butylamine (5)	$P(^tBu)_3HBF_4$	5	--, 0:0:100
9	$Pd(OAc)_2$	Butylamine (5)	BrettPhos	5	--, 37:63:0
10	$Pd(OAc)_2$	Butylamine (5)	BrettPhos	14	--, 40:60:00
11	$Pd(OAc)_2$	*N*-Boc-Butylamine (5)	RuPhos	5	Decomposition
12	$Pd(OAc)_2$	*N*-Boc-Butylamine (5)	BrettPhos	5	Decomposition
13	$Pd(OAc)_2$	Butylamine (5)	RuPhos	5[b]	72%, 21:21:58
14	$Pd(TFA)_2$	Butylamine (5)	BrettPhos	5[b]	19%, 68:32:0
15	$Pd_2(dba)_3$	Butylamine (5)	BrettPhos	5[b]	47%, 26:74:0
16	$Pd(Br)_2$	Butylamine (5)	BrettPhos	5[b]	33%, 30:70:0
17	$Pd(acac)_2$	Butylamine (5)	BrettPhos	5[b]	42%, 60:40:0

[a]Reported yields are NMR yields. [b]Cs_2CO_3 was used instead of LiO^{t}Bu

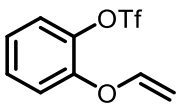
4.6 Conclusion

In this chapter we have provided early data for three unique Pd-catalyzed alkene difunctionalization projects that show early promise. The construction of dihydrobenzofurans, the expansion of carbon nucleophile scope with nitrile carbanions, and expansion of amine nucleophile scope in our regiodivergent cyclization will increase access to complex products that would be challenging to make with other methods.

4.7 Experimental

General Considerations: All reactions were carried out under a nitrogen atmosphere in vacuum and flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The substrates **4-5**,[9a] **4-7**,[9a] **4-11**,[3.11] Experimental and N-(2-pyridyl)triflimide[14] were prepared by previously published methods. Alkenyl triflate starting materials were stored in a freezer under nitrogen. Bulk quantities of cesium carbonate, lithium *tert*-butoxide, and lithium hexamethyldisilazide were stored in nitrogen-filled glove box and small amounts were removed within a few days of use. Toluene, tetrahydrofuran, dichloromethane, and diethyl ether were purified using a GlassContour solvent purification system. Anhydrous 1,4 dioxane was purchased from Sigma-Aldrich and was used without purification. Structural and stereochemical assignments were made on the basis of 2-D COSY. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted.

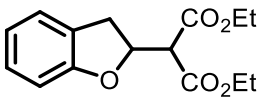
Preparation and Characterization of Substrates



2-(vinyloxy)phenyl trifluoromethanesulfonate (4-1) A vacuum flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 2-(vinyloxy)phenol (5 mmol, 0.68 g, 1 equiv) dissolved in DCM (10 mL, 0.5 M). Pyridine (6 mmol, 485 µL, 1.2 equiv) was added to the flask. The reaction was cooled to 0 °C. Triflic anhydride (5.5 mmol, 925 µL, 1.1 equiv) was added to the flask and the reaction warmed to rt and allowed to react overnight (15 h). The reaction was quenched with aqueous ammonium chloride (15 mL). The mixture was stirred briefly then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 98:2 -> 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 0.74 g (55%) of the title compound as a yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.39–7.25 (m, 2 H) 7.19–7.09 (m, 2 H) 6.69–6.55 (m, 1 H) 4.95–4.83 (m, 1 H) 4.60 (dd, *J* = 6.0, 2.1 Hz, 1 H).

Preparation and Characterization of Products



diethyl 2-(2,3-dihydrobenzofuran-2-yl)malonate (4-4) A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 1.8 mg, 0.04 equiv), $P(cy)_3HBF_4$ (0.012 mmol, 4.4 mg, 0.06 equiv), and lithium *tert*-butoxide (0.28 mmol, 22.4 mg, 1.4 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. **4-1** (0.2 mmol, 53.6 mg, 1.0 equiv) was weighed in a dram vial and diluted with toluene (1 mL, 0.2M). This mixture was added to

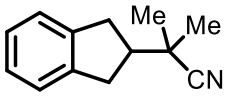
the Schlenk tube and diethyl malonate (0.24 mmol, 37 µL 1.2 equiv) was added. Toluene (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 95 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 50:50 DCM:hexanes as the eluent. This procedure afforded 15 mg (27%) of the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.3 Hz, 1 H) 7.10 (t, *J* = 7.7 Hz, 1 H) 6.85 (t, *J* = 7.4 Hz, 1 H) 6.77 (d, *J* = 8.0 Hz, 1 H) 5.33 (td, *J* = 9.0, 6.6 Hz, 1 H) 4.34–4.11 (m, 4 H) 3.74 (d, *J* = 8.8 Hz, 1 H) 3.47 (dd, *J* = 16.1, 9.3 Hz, 1 H) 3.12 (dd, *J* = 16.0, 6.6 Hz, 1 H) 1.32–1.21 (m, 6 H).

General Procedure for Palladium-Catalyzed Alkene Difunctionalizations with Nitrile Nucleophiles, General Procedure A

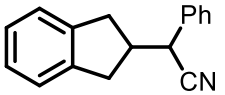
A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with Pd(BrettPhos)(allyl)Cl (0.008 mmol, 8.6 mg, 0.04 equiv), BrettPhos (0.012 mmol, 6.4 mg, 0.06 equiv), and Lithium bis(trimethylsilyl)amide (0.44 mmol, 73.6 mg, 2.2 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. **4-5** (0.2 mmol, 53.2 mg, 1.0 equiv) was weighed in a dram vial and diluted with 1,4 dioxane (1 mL, 0.2M). This mixture was added to the Schlenk tube and the nitrile nucleophile (0.24 mmol, 1.2 equiv) was added. 1,4 dioxane (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk

tube was then heated to 95 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel.



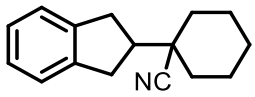
2-(2,3-dihydro-1H-inden-2-yl)-2-methylpropanenitrile (4-6b) The title compound was prepared using General Procedure A with isobutyronitrile (0.24 mmol, 22 µL, 1.2 equiv). The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 11.5 mg (31%) of the title compound as a yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2 H) 7.18–7.12 (m, 2 H) 3.08 (dd, *J* = 15.2, 8.4 Hz, 2 H) 2.96 (dd, *J* = 15.5, 10.0 Hz, 2 H) 2.48 (tt, *J* = 10.0, 8.3 Hz, 1 H) 1.43 (s, 6 H).



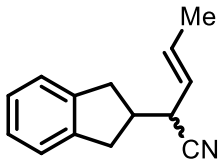
2-(2,3-dihydro-1H-inden-2-yl)-2-phenylacetonitrile (4-6c) The title compound was prepared using General Procedure A with phenylacetonitrile (0.24 mmol, 28 mg, 1.2 equiv). The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 7 mg (15%) of the title compound as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.47–7.33 (m, 5 H) 7.24–7.12 (m, 4 H) 3.83 (d, *J* = 8.0 Hz, 1 H) 3.16 (dd, *J* = 15.2, 7.2 Hz, 1 H) 3.08–2.86 (m, 3 H) 2.77 (dd, *J* = 15.3, 7.5 Hz, 1 H).



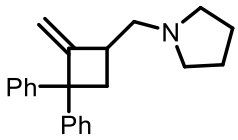
2-(2,3-dihydro-1H-inden-2-yl)-2-phenylacetonitrile (4-6d) The title compound was prepared using General Procedure A with cyclohexane carbonitrile (0.24 mmol, 26 mg, 1.2 equiv). The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 24.3 mg (54%) of the title compound as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2 H) 7.18–7.12 (m, 2 H) 3.11–2.90 (m, 4 H) 2.45 (tt, *J* = 10.2, 8.4 Hz, 1 H) 2.14–2.03 (m, 1 H) 1.85–1.55 (m, 6 H) 1.41–1.30 (m, 2 H) 1.29–1.18 (m, 1 H).



(E)-2-(2,3-dihydro-1H-inden-2-yl)pent-3-enenitrile (4-6e) The title compound was prepared using General Procedure A with 3-pentenenitrile (0.24 mmol, 20 mg, 1.2 equiv). The crude material was purified via column chromatography on silica gel using 95:5 hexanes:ethyl acetate as the eluent. This procedure afforded 3 mg (7%) of the title compound as mixture of 2:1 diastereomers and as a colorless oil. ^{1}H NMR peaks reported for the mixture.

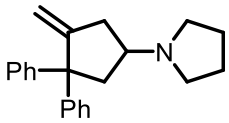
^{1}H NMR (401 MHz, $CDCl_3$) δ 7.25–7.11 (m, 4 H) 5.94–5.74 (m, 1 H) 5.45–5.35 (m, 1 H) 3.56–3.46 (m, 0.5 H) 3.34–2.67 (m, 5 H) 1.78–1.74 (m, 1.33 H) 1.69–1.65 (m, 1.87 H).



1-((2-methylene-3,3-diphenylcyclobutyl)methyl)pyrrolidine (4-12a) A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 1.8 mg, 0.04 equiv), $P(^tBu)_3HBF_4$ (0.012 mmol, 3.5 mg, 0.06 equiv), and lithium *tert*-butoxide (0.28 mmol, 22.4 mg, 1.4 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. **4-11** (0.2 mmol, 76.5 mg, 1.0 equiv) was weighed in a dram vial and diluted with toluene (1 mL, 0.2M). This mixture was added to the Schlenk tube and pyrrolidine (0.24 mmol, 20 µL 1.2 equiv) was added. Toluene (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 95 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 25:75 (3:1 ethyl acetate:ethanol):hexanes as the eluent. The isolated material was dissolved in ethyl acetate and tosic acid (0.24 mmol, 41 mg, 1.2 equiv) was added. The solution was stirred briefly then allowed to crystalize overnight. The crystals were collected and recrystallized in 15:1 ethyl acetate:ethanol. The crystals were dissolved in aqueous NaOH (2 mL, 1 M) and the organics were extracted with DCM. Solvent was removed under vacuum. This procedure afforded 12.1mg (20%) of the title compound as a yellow oil.

^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2 H) 7.25–7.21 (m, 2 H) 7.21–7.15 (m, 2 H) 7.15–7.10 (m, 3 H) 7.10–7.05 (m, 1 H) 5.09 (d, *J* = 2.4 Hz, 1 H) 4.95 (d, *J* = 2.8 Hz, 1 H) 3.17–3.04 (m, 1 H) 2.85–2.73 (m, 2 H) 2.60 (dd, *J* = 10.8, 8.6 Hz, 1 H) 2.50 (dd, *J* = 12.1,

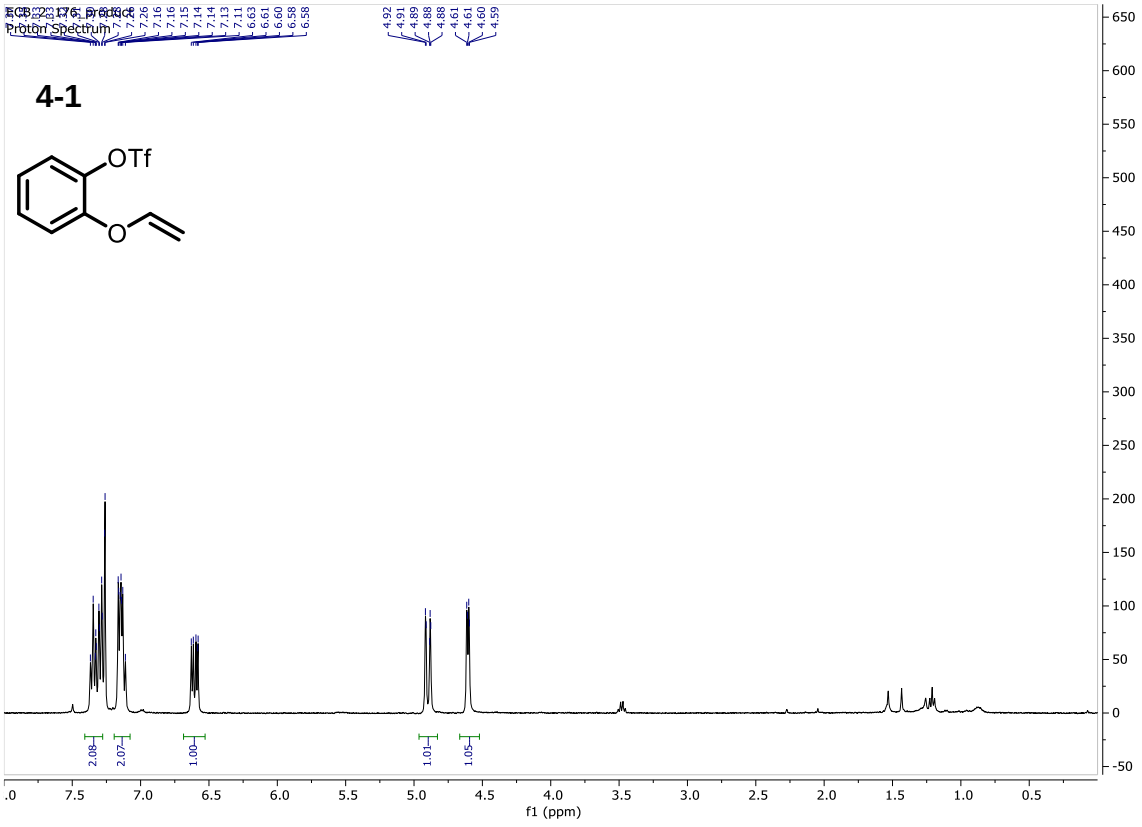
9.5 Hz, 1 H) 2.47–2.35 (m, 4 H) 1.78–1.64 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.03, 146.65, 146.60, 128.27, 128.11, 127.63, 127.31, 126.12, 125.87, 106.42, 59.85, 58.68, 54.59, 39.70, 39.56, 23.51.

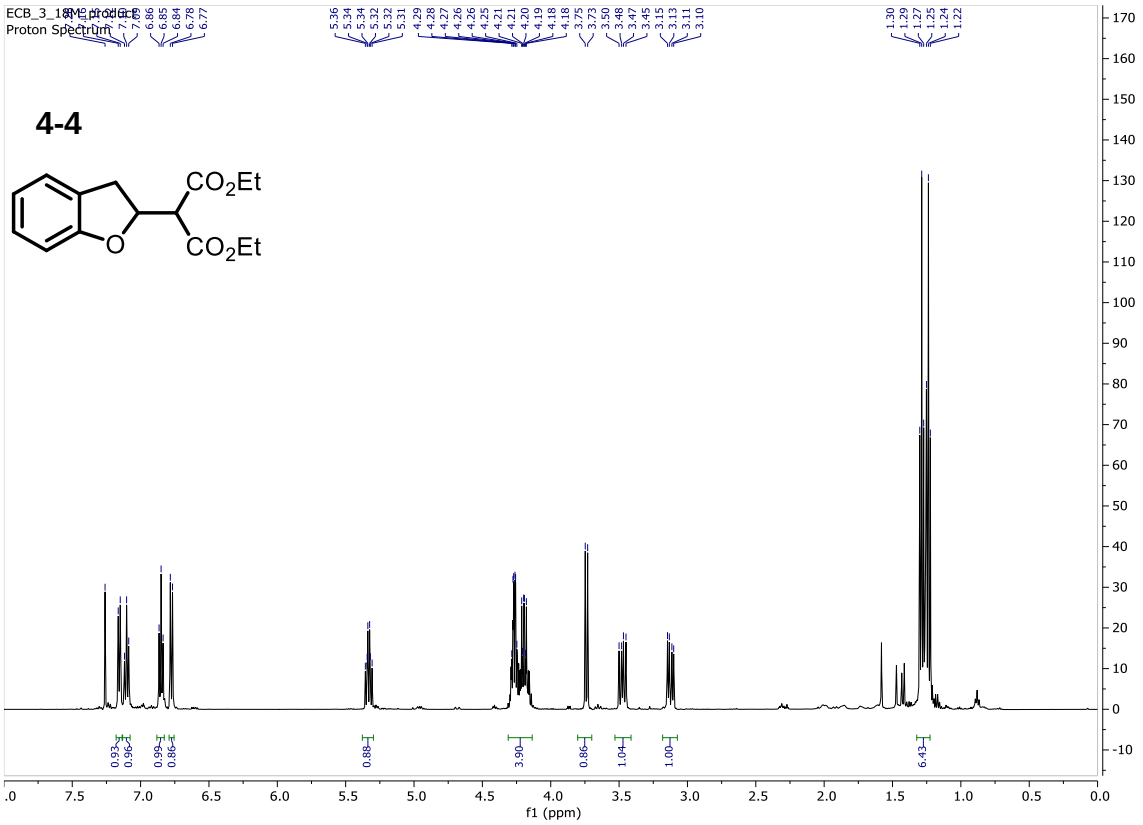


1-(4-methylene-3,3-diphenylcyclopentyl)pyrrolidine (4-13a) A vacuum and flame-dried 10 mL Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 1.8 mg, 0.04 equiv), BrettPhos (0.012 mmol, 6.4 mg, 0.06 equiv), and lithium *tert*-butoxide (0.28 mmol, 22.4 mg, 1.4 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. **4-11** (0.2 mmol, 76.5 mg, 1.0 equiv) was weighed in a dram vial and diluted with toluene (1 mL, 0.2M). This mixture was added to the Schlenk tube and pyrrolidine (0.24 mmol, 20 µL 1.2 equiv) was added. Toluene (1 mL, 0.2M) was used to rinse the dram vial and the solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 95 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 1 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 25:75 (3:1 ethyl acetate:ethanol):hexanes as the eluent. The isolated material was dissolved in ethyl acetate and tosic acid (0.24 mmol, 41 mg, 1.2 equiv) was added. The solution was stirred briefly then allowed to crystalize overnight. The crystals were collected and recrystallized in 15:1 ethyl acetate:ethanol. The crystals were dissolved in aqueous NaOH

(2 mL, 1 M) and the organics were extracted with DCM. Solvent was removed under vacuum. This procedure afforded 6 mg (10%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.21 (m, 4 H) 7.20–7.11 (m, 3 H) 7.10–7.04 (m, 1 H) 7.03–6.98 (m, 2 H) 5.19–5.12 (m, 1 H) 4.56–4.45 (m, 1 H) 2.77–2.67 (m, 2 H) 2.54–2.35 (m, 7 H) 1.79–1.66 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.64, 147.16, 145.92, 128.49, 128.43, 128.39, 128.12, 128.09, 127.79, 126.17, 125.87, 111.67, 62.09, 60.33, 53.16, 47.99, 39.15, 23.36.

4.8 Unpublished Spectra

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4-4
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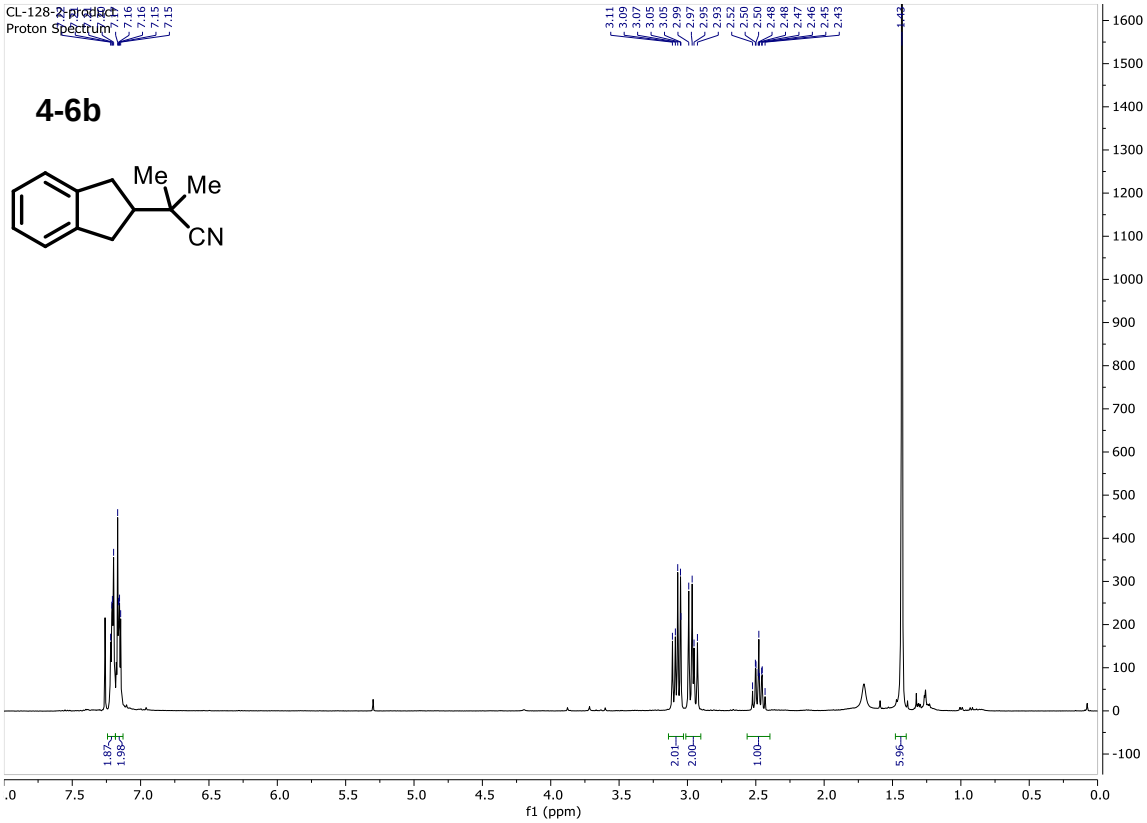
CO2Et
O
f1 (ppm)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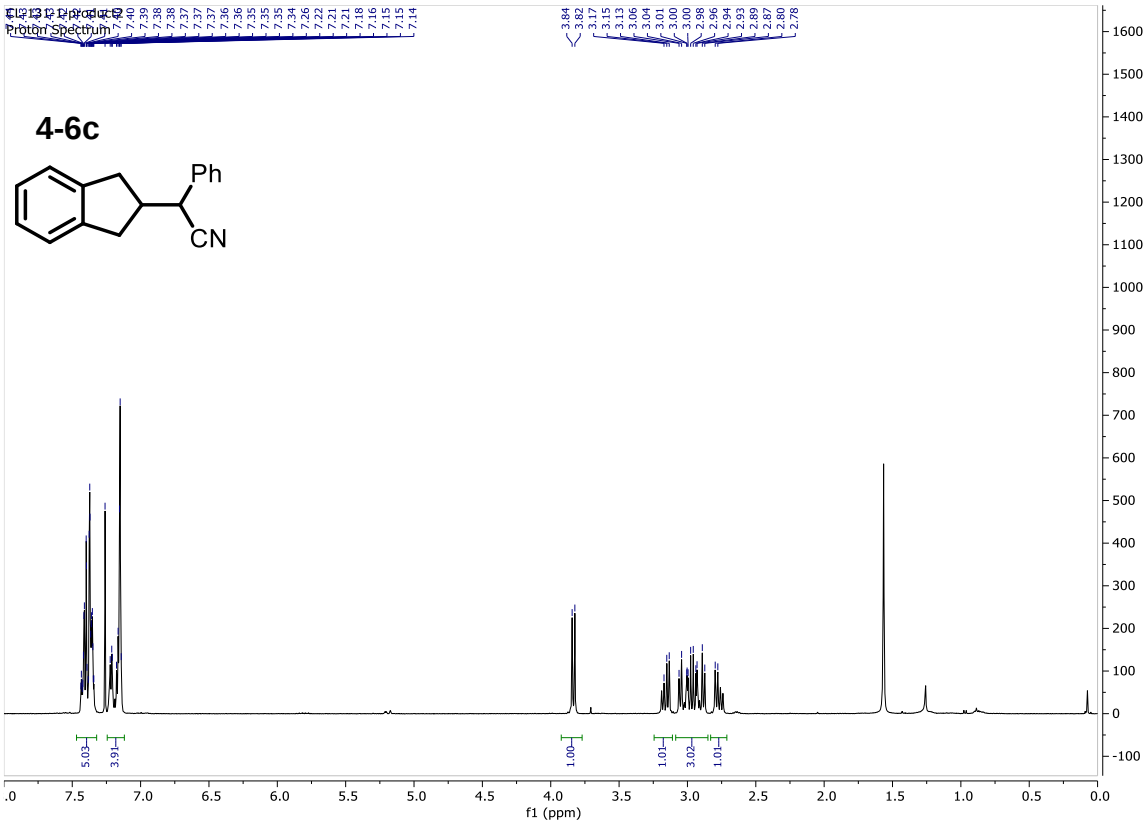
Me
CN
f1 (ppm)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Ph
CN
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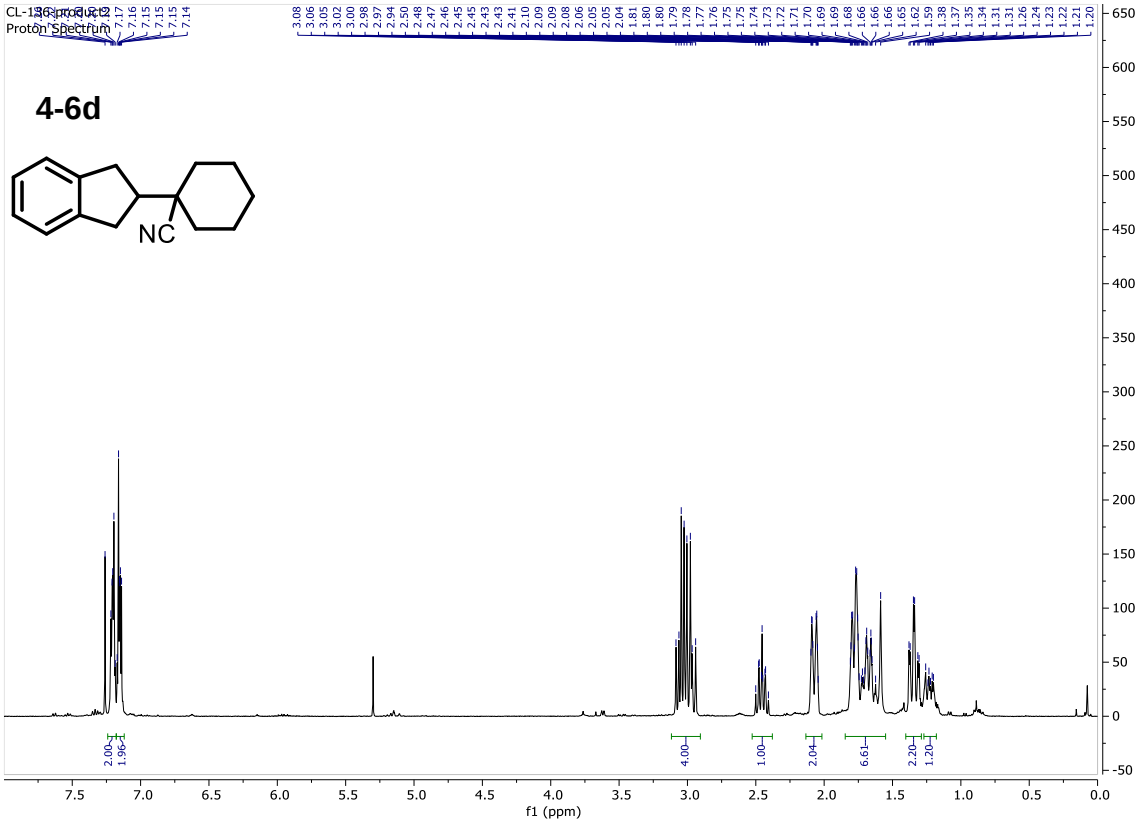
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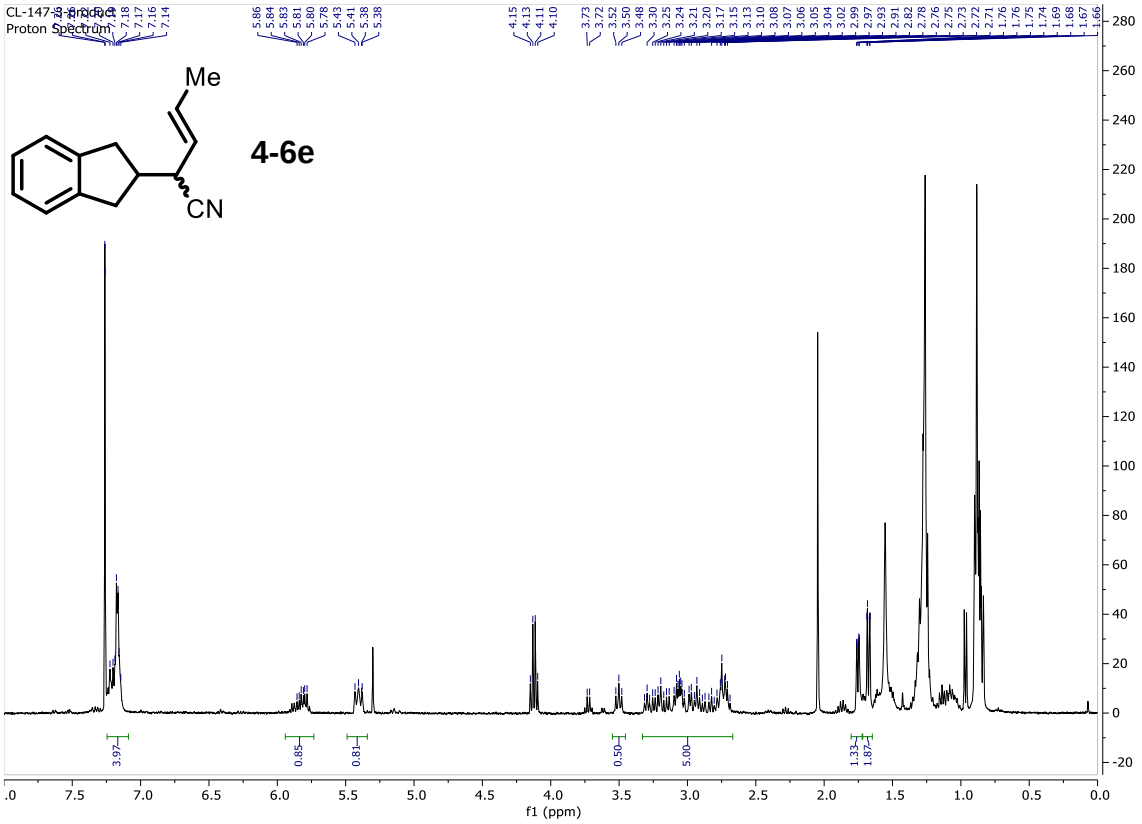
4-6d
NC
f1 (ppm)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CN
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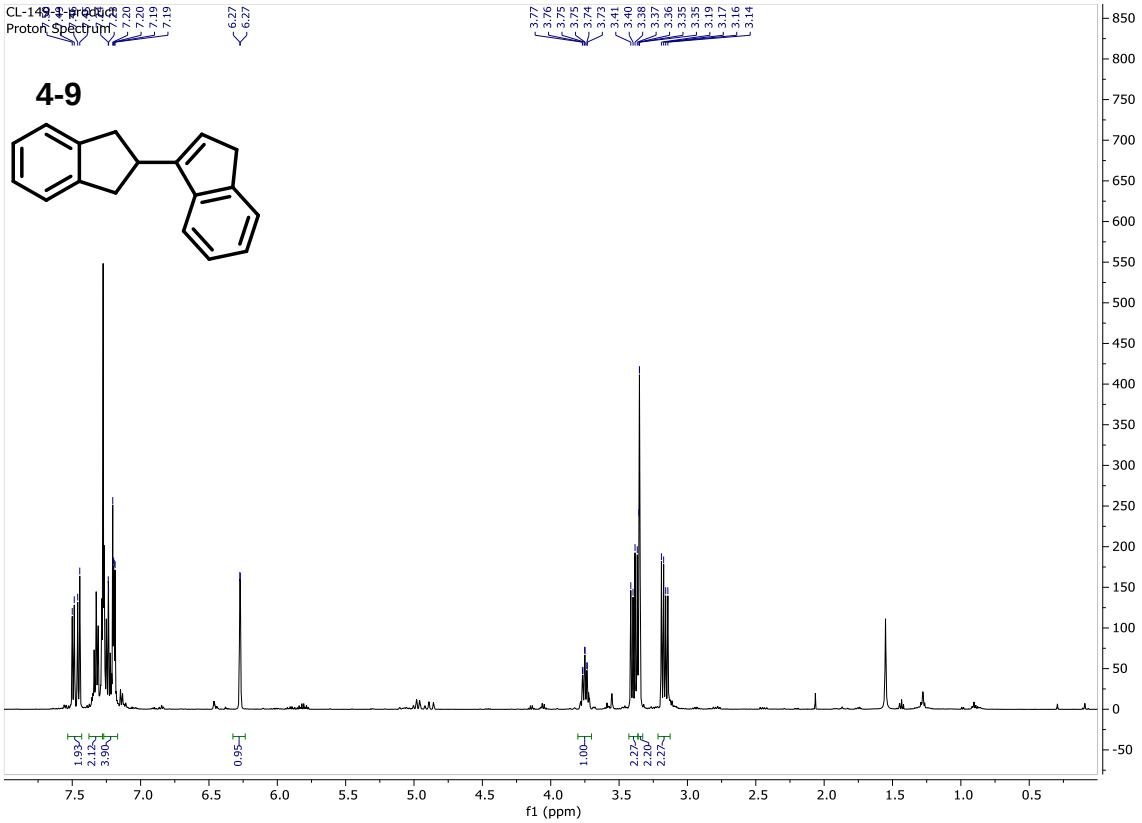
f1 (ppm)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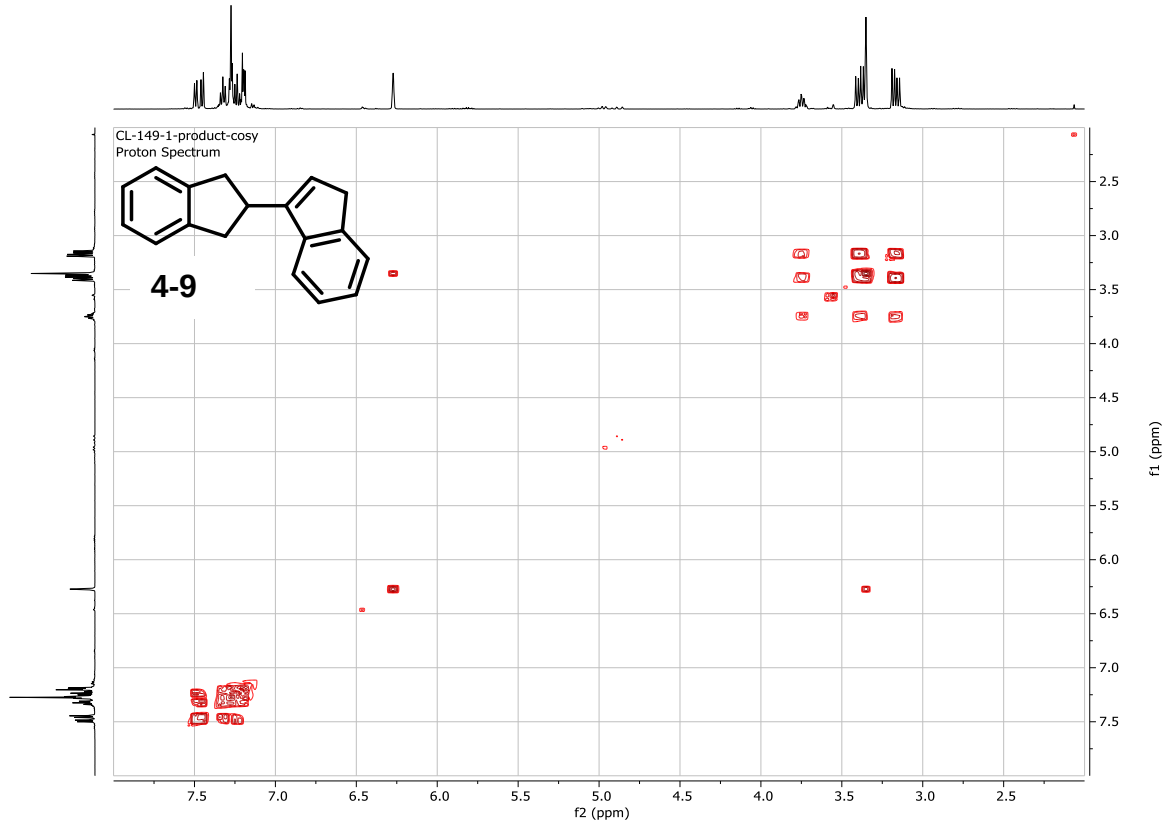
4-9
f1 (ppm)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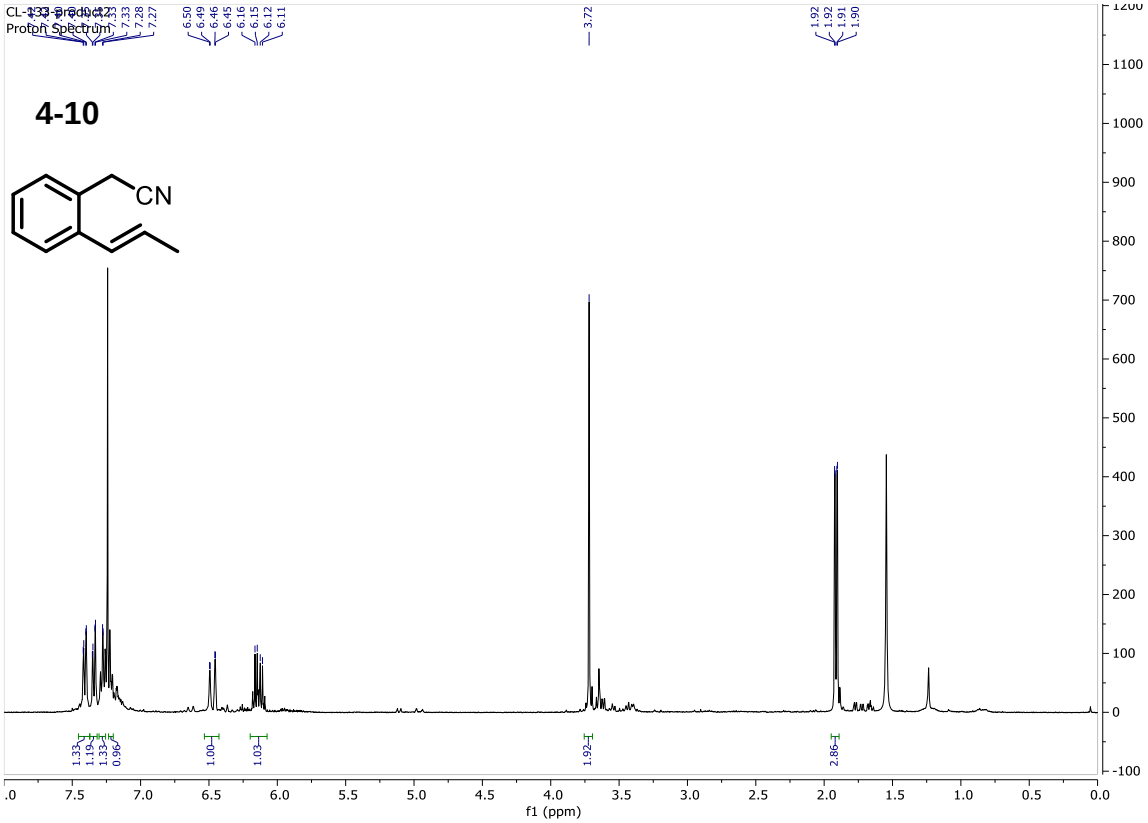
f1 (ppm)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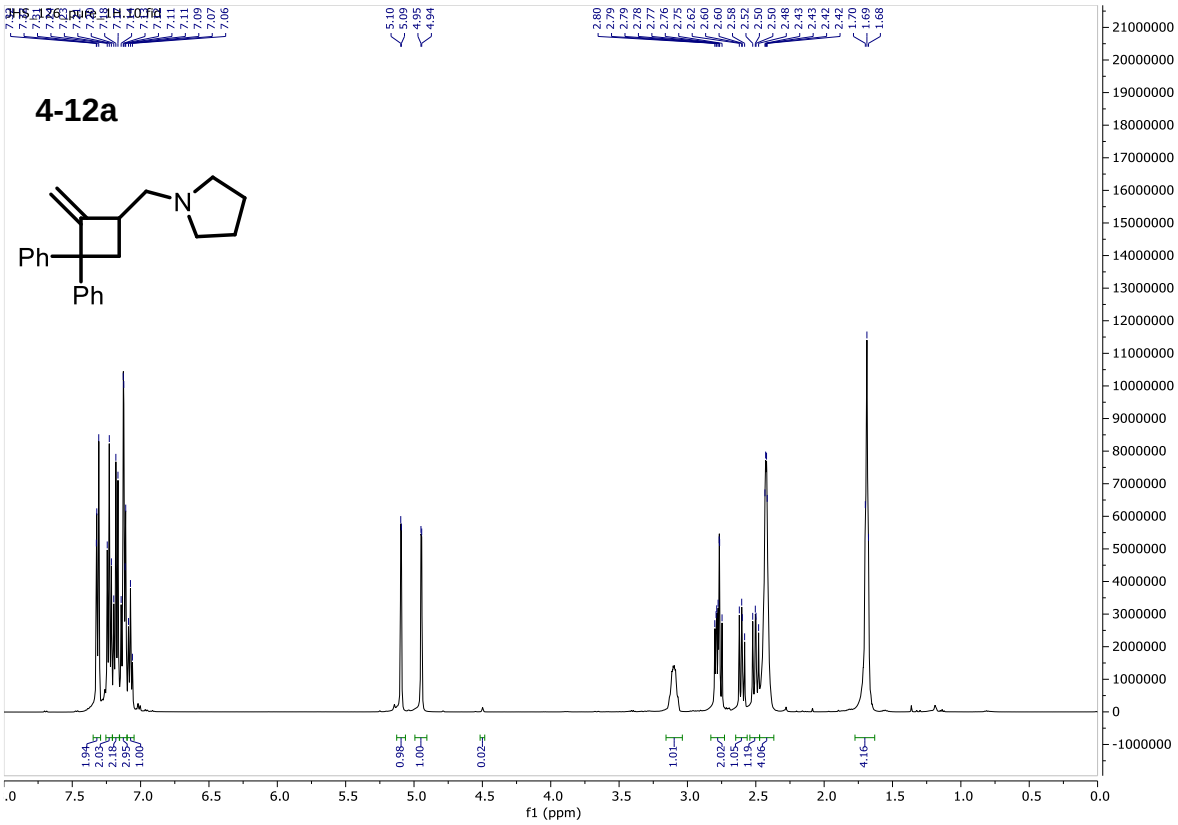
CN
f1 (ppm)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Ph
N
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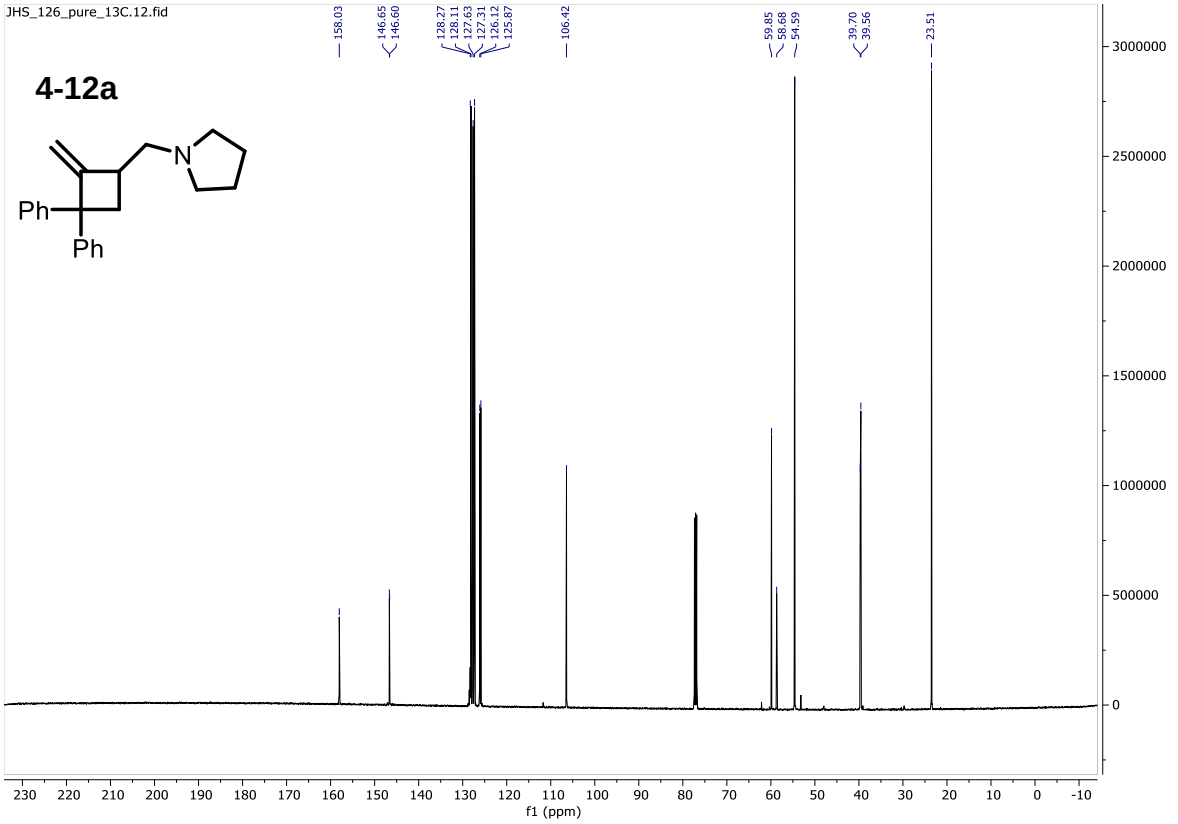
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Ph
N
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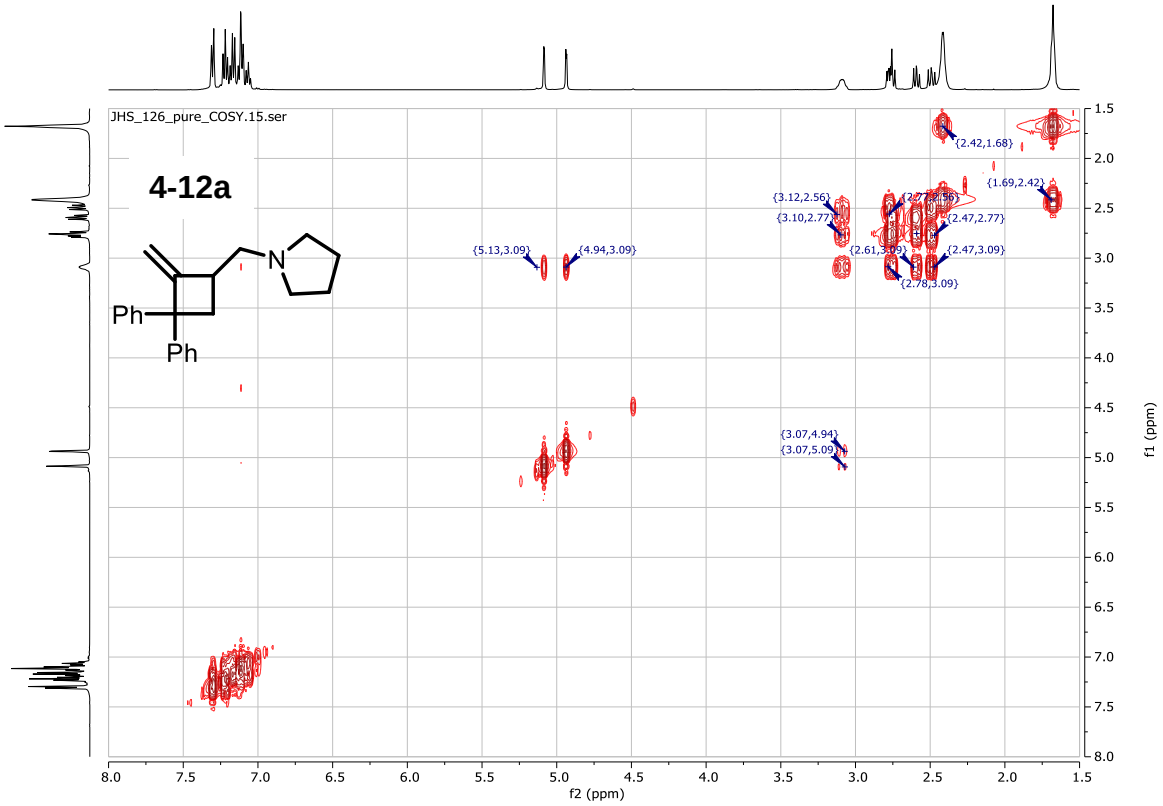
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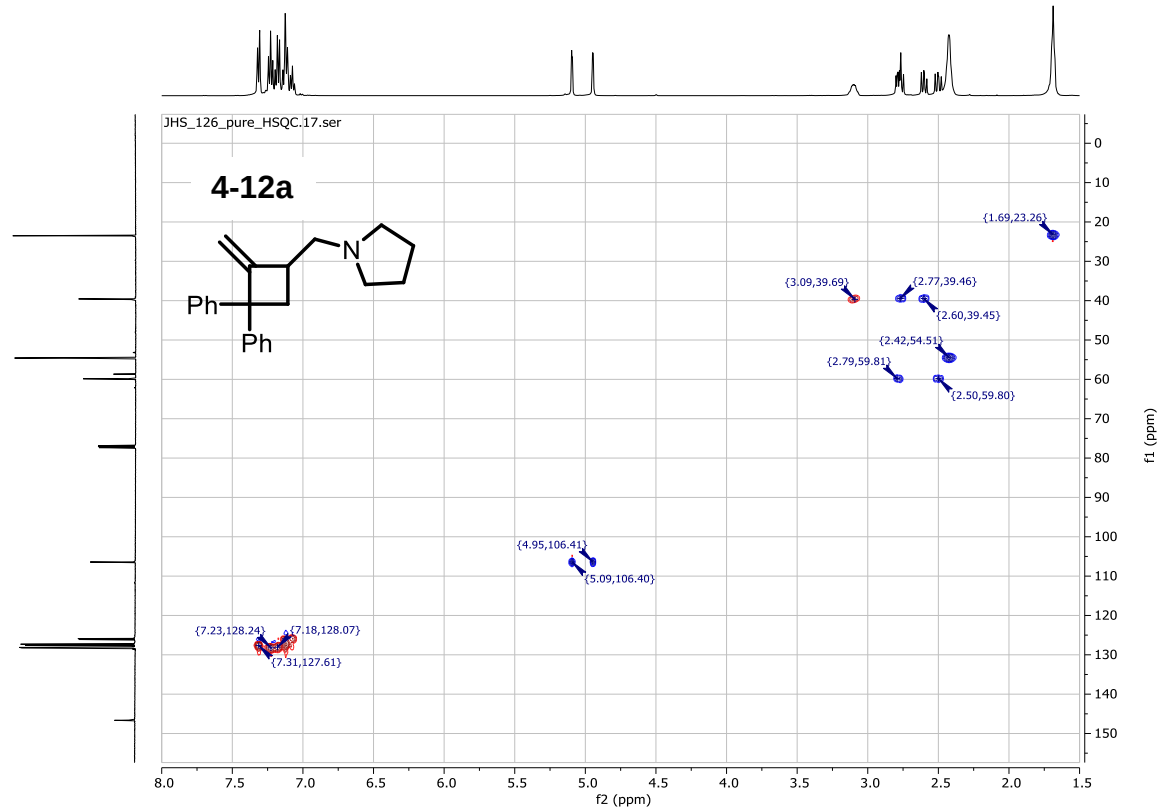
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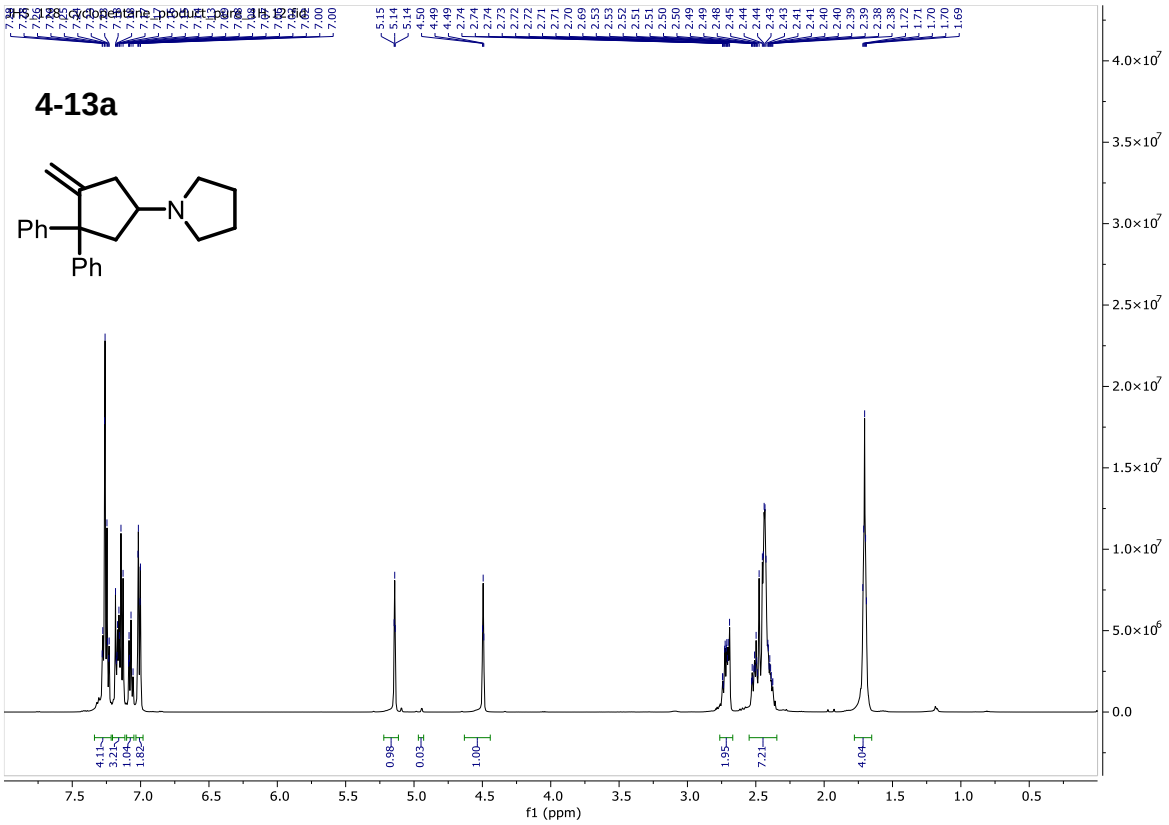
f2 (ppm)
f1 (ppm)


4-13a
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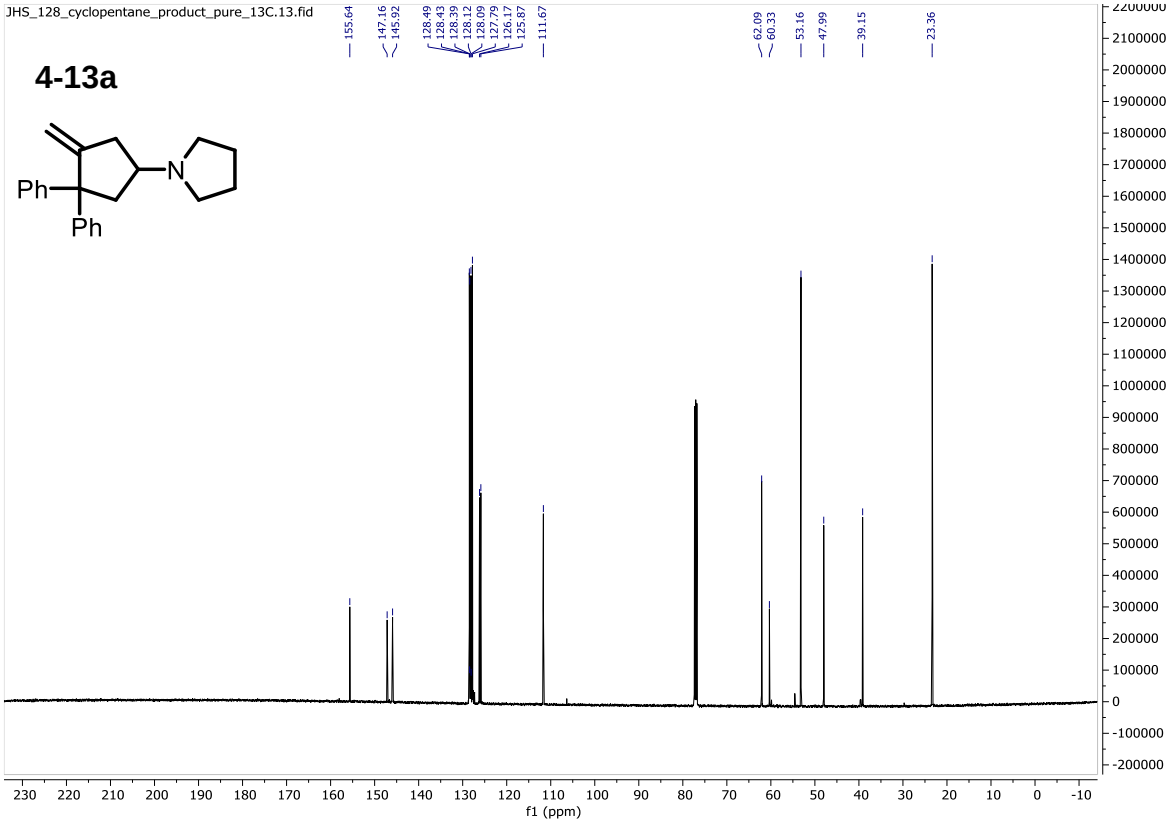
Ph
N
f1 (ppm)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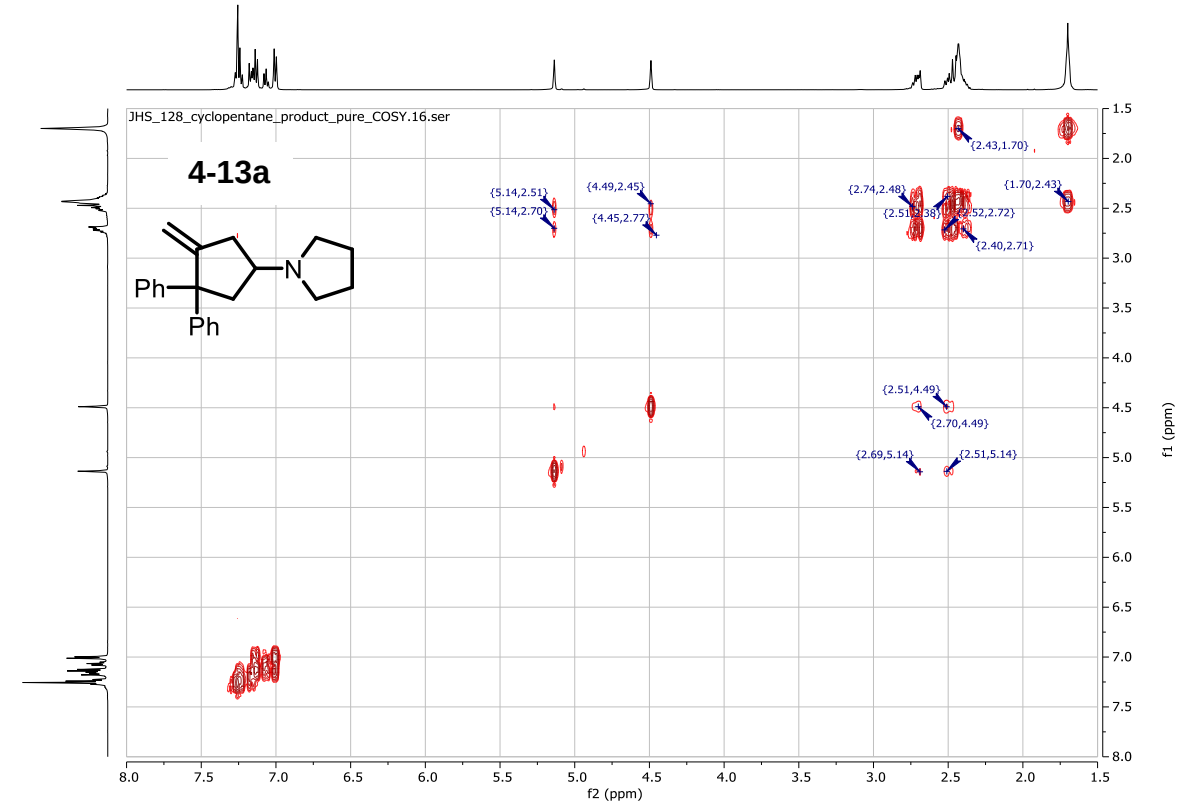
Ph
Ph
N
f1 (ppm)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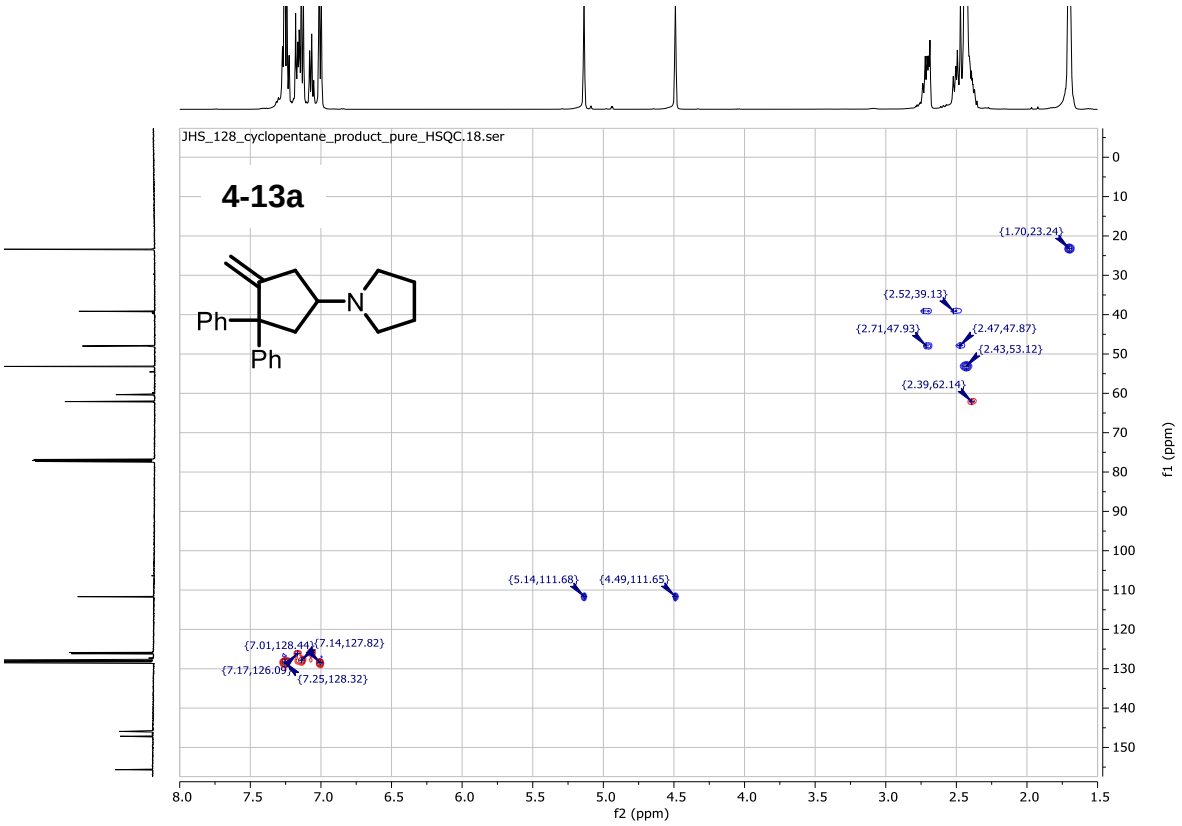
f2 (ppm)
f1 (ppm)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f2 (ppm)
f1 (ppm)

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